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THE TREATMENT OF CONGESTIVE HEART FAILURE

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FOR purposes of practical therapeutics, congestive heart failure can be divided into two types. In the more common of these, decompensation is the result of intrinsic myocardial disease. For all cases of this kind treatment is the same regardless of underlying etiology. In the less common form, failure is due, not to primary myocardial damage, but to some systemic disease or local pathologic disorder which either increases the demands on the heart for work or interferes with the ability of the myocardium to maintain adequate circulation. Examples of this form of decompensation are cases due to thyrotoxicosis, myxedema, beriberi, severe anemia, arteriovenous aneurysm, patent ductus arteriosus, coarctation of the aorta and chronic constrictive pericarditis. In this group treatment by the measures employed in the common form of failure is of no lasting value. A satisfactory result depends on the medical or surgical correction of the causative condition, and a number of notable advances have been made along this line within the past several years. Parallel with this progress, intensive research on the pathologic physiology of the common type of decompensation has resulted in important changes in therapy. Today, as a result, most persons suffering from an initial attack of the common form of failure can be restored to a comfortable and useful state of health and often can be maintained in this condition for many years by careful supervision of activities, diet, medication and living habits. Treatment of the more common type of congestive failure will be the subject of the remainder of this discussion.

Rest. A period of strict rest is an essential part of the management of every case of myocardial failure, and with few exceptions the first part of this period should be spent in bed. Levine[1] has pointed out that the sudden enforcement of the conventional type of bed rest may have harmful effects. These are to be regarded as complications against which suitable precautions must be taken, and the possibility of their occurrence does not detract from the importance of rest itself. In patients with congestive failure, the recumbent position, through the effect of gravity, brings about a shift of edema fluid from the lower to the upper portions of the body. This often results in prompt diminution in the edema of the lower extremities, but, unless proper treatment has been instituted, edema may simultaneously appear or increase over the back and the evidence of pulmonary congestion may become more apparent. Hydrothorax may develop for the first time. The recumbent position also facilitates the return flow of blood to the heart and, by favoring absorption of edema fluid from the legs into the blood stream, results in an increase in circulating blood volume.[2] The load upon the heart is therefore augmented, and unless corrective steps are taken a decided increase in the degree of failure

may result. These undesirable effects can be avoided by prompt and vigorous treatment with digitalis and diuretic drugs, and, in patients with severe decompensation and considerable edema, by the use of shock blocks or kitchen chairs under the head of the bed. The latter measures were proposed by Levine, and their use readily convinces one of their value.

Except for the use of a commode at the bedside, rest in bed is continued until the patient has become comfortable and has lost most of his edema. He is then allowed up in a chair for as long each day as he desires but is assisted in and out of bed. In cases of more than mild degree, no additional privileges are granted for from four to six weeks. Gradually increasing activity is then permitted, but precautions must be taken to avoid dyspnea and fatigue, and there must be careful observation for gain in weight and any return of edema.

Digitalis. Digitalis remains the most valuable drug in the treatment of congestive heart failure. Every patient suffering from failure should be completely digitalized, and with few exceptions the digitalized state should then be maintained permanently. Digitalis leaf may be administered in pills, tablets or capsules whose potency has been adjusted to conform to the international standard, or one may employ one of the purified glycosides, such as digitoxin. The dosage schedule ordered in any instance is determined entirely by the urgency with which the effect of digitalis is needed. The purified glycosides have no special advantage over whole digitalis leaf, either in the way of clinical effectiveness or in simplicity of dosage. The aim in administering any preparation of digitalis is to secure the maximum therapeutic effect of the drug without producing toxic symptoms. The established average amounts necessary to attain this goal are of value only as a general guide, and the amount actually administered in any case must be individualized for the particular patient being treated. Maintenance of a satisfactory state of digitalization often is more difficult with purified glycosides than with the whole leaf. The reason for this is that certain of the purified preparations are excreted more rapidly than are the products of the whole leaf, and others are eliminated much more slowly with a consequent tendency to cumulate in the body.

When auricular fibrillation is present, the ventricular rate furnishes the most helpful guide as to whether or not the maximum therapeutic effect of digitalis has been obtained. The drug is given in amounts sufficient to reduce the rate, in the absence of fever, severe anemia and hyperthyroidism, to approximately 70 beats per minute. When normal rhythm is present, the heart rate is of no aid in estimating the degree of digitalization, and one must then prescribe the amount of the drug required by the average patient and be guided by the general clinical response. Once the patient has been satisfactorily digitalized, this state usually can be maintained by the administration of 0.1 Gm. of the whole leaf on five to seven days of each week.

There are no contraindications for the administration of digitalis to patients who have congestive heart failure. In the presence of frequent ventricular premature beats or auriculoventricular block of either first or second degree, however, digitalization should be accomplished gradually and with electrocardiographic control. It has long been considered dangerous to employ

digitalis in patients suffering from ventricular paroxysmal tachycardia, the fear being that the drug, by increasing the irritability of the myocardium, might convert the arrhythmia to ventricular fibrillation. This apprehension now appears to have been needless. The treatment of choice for ventricular tachycardia consists of efforts to abolish the disturbance by the oral or intravenous administration of quinidine or Pronestyl®. If in spite of these drugs the arrhythmia persists and signs of decompensation appear, digitalis should be given in an effort to support the failing myocardium.

The oral route of administration is the one of choice for digitalis and can be employed in all but an occasional patient. At times, a condition is present which causes vomiting or prevents the taking of drugs by mouth, and intramuscular injection must then be resorted to. Several preparations are available for use in this manner. For those which contain one cat unit of digitalis in 2 cc. of solution, an initial dose of 10 cc. can be followed in four to six hours by a second injection of the same amount. The process of digitalization is then completed by administering 2 cc. two or three times a day until the full effect of the drug is obtained.

The absorption of digitalis from muscular tissue is no more rapid than is absorption from the gastrointestinal tract. In true cardiac emergencies, therefore, where a delay of even a few hours in securing the effect of the drug might mean the difference between a successful and a fatal outcome, intravenous administration of a digitalis preparation is indicated. Instances of this kind are uncommon. The preparations mentioned for intramuscular use may be given also by intravenous injection, and the dosage is the same by either route. If one prefers, ouabain, digitoxin, or Cedilanid® can be employed. When ouabain is used, the initial dose is usually 0.5 mg., and this is followed by additional injections of 0.1 mg. to 0.25 mg. every four to six hours until a total of not more than 1.0 mg. has been given. For digitoxin, intravenous dosage is the same as for oral administration, namely 0.8 mg. (4 cc.) followed in four to six hours by 0.4 mg. If Cedilanid® is employed, 0.8 mg. (4 cc.) usually is given initially, followed in four to six hours by a second injection of 0.4 mg. to 0.8 mg. After one of these schedules has been finished, the process of digitalization is completed by oral administration of digitalis or, if this is not possible, by intramuscular injection of a suitable preparation in the manner already outlined. It is, of course, essential to be certain that patients to whom ouabain or digitalis preparations are to be given intravenously have not received digitalis during the preceding two weeks.

Diet. The most significant change in the treatment of congestive heart failure in recent years has been the adoption of diets of restricted sodium content. Formerly it was customery to limit the fluid intake of patients suffering from cardiac decompensation and pay little attention to the amount of salt in the food. This has been changed entirely as a result of repeated demonstration that sodium retention on a renal basis is a cardinal feature of congestive failure and the most important factor responsible for water retention and the development of edema. There is uniform agreement today that the diet of patients with myocardial failure should contain not more than 500 mg. of

sodium per 24 hours. Restriction of fluids is unnecessary and may even be harmful. The most satisfactory results are obtained when the patient takes between 2 and 3 L. of water daily, and whenever an individual is unable to drink this much, it appears advisable to administer sufficient 5 per cent glucose solution in distilled water by intravenous drip to bring the total fluid intake up to the desired level.

The preparation of a low sodium diet can be accomplished in the home without great difficulty if specific instructions are given. No salt is used in cooking, all salted foods are eliminated, and only salt-free bread and unsalted or washed butter are allowed. Canned foods to which salt has been added during processing, and all foods prepared with baking soda or baking powder are prohibited. Medicines and proprietary preparations which contain sodium must not be used. A sodium free salt substitute may be taken if desired.

In patients who respond well to treatment and maintain a satisfactory state as they increase their activities, the limitation of sodium intake often can be lightened. Only occasionally, however, can the daily allowance be increased beyond 1500 mg.

Diuretics. Although many individuals who have congestive failure will recover satisfactorily when treated by means of rest, digitalis, and a low sodium diet without other measures, the additional use of diuretic drugs hastens improvement and more promptly restores the patient to a state of comfort. Their administration, therefore, is indicated in every case. The most effective preparations for routine use are the organic mercurial compounds, and of the members of this group Mercuhydrin® is the one most extensively employed at present. This preparation can be given by intravenous or intramuscular injection, but the intramuscular route is preferred because of its greater safety.

In the early stages of treatment, mercurial diuretics are given daily, the initial dose of 0.5 cc. being increased to 1.0 cc. and then to 2.0 cc. whenever the patient fails to lose three pounds in 24 hours. Gold and his associates[3] have demonstrated that daily injections can be given safely to all persons in whom the output of urine is within normal limits. Excessive diuresis should be guarded against, especially in elderly individuals, because of its prostrating effect, the danger of inducing the "low salt syndrome" and azotemia, and because rapid dehydration may favor the development of phlebothrombosis and subsequent pulmonary embolism. After all edema has disappeared and the daily injection fails to cause further diuresis and loss in weight, the interval between doses is lengthened gradually, and in favorable cases the drug is eventually discontinued.

Although reactions to Mercuhydrin® are not common, there is one type which seems to have increased in incidence since it has become such standard practice to administer the drug at frequent intervals. Reactions of this kind appear to be due to the development of hypersensitivity to the mercurial component of the drug. Whitman and Proudfit[4] observed that they occur only after a series of 6 to 11 daily intramuscular injections. In the fully developed form, the reactions are characterized by fever, often preceded by a chill and usually accompanied by muscular aching and general malaise. In some patients

there also is nausea, vomiting, pain in the abdomen or anterior chest, or transient erythema of the face, neck and upper trunk. The symptoms usually last for 12 hours or less but recur with increasing severity after each subsequent administration of the drug. Because the first evidence of developing hypersensitivity of this kind usually consists of mild fever of short duration, close attention should be paid to the temperature chart whenever mercurial diuretics are being given at daily intervals. Changing to a different mercurial preparation avoids further trouble.

It is seldom necessary or advantageous to administer ammonium chloride simultaneously with a mercurial diuretic. Ammonium chloride is helpful at times, however, in doses of 4 to 8 Gm. daily, in preventing a return of edema after the patient has become ambulatory. Its effectiveness may possibly be increased by giving it for four consecutive days followed by a rest period of three or four days.

Cation Exchange Resins. A recent addition to the treatment of congestive heart failure and one of considerable interest has been the use of cation exchange resins. These substances have the capacity to take up sodium in limited amounts in the intestinal tract, and in certain patients their administration permits liberalization of the sodium content of the diet. It must be emphasized, however, that resin is not a complete substitute for salt restriction for, in spite of its use, sodium intakes of more than 1500 mg. daily usually result in reappearance of edema.

Klingensmith and Elkinton[5] have pointed out situations in which cation exchange resins are often helpful. In patients in whom congestive heart failure resists the usual measures of treatment, the addition of resin may result in diminution of edema. In others, who respond satisfactorily to treatment but require periodic injections of a mercurial diuretic to remain free from edema, the administration of resin may substitute partially or completely for the diuretic drug. Finally, persons who are hypersensitive to mercurial diuretics may experience diuresis and diminution in edema from the use of exchange resin. Unfortunately, about one-half of the patients to whom resin is administered experience anorexia, nausea, vomiting, abdominal cramps, diarrhea or constipation; and in many these symptoms are of sufficient severity to force discontinuing the preparation.

Resin should not be given to patients who have renal failure. If this precaution is taken and if a combination of ammonium and potassium cycle resins is employed, important alterations in the potassium content of the blood serum need not be anticipated. Adequate calcium and a mixed vitamin preparation should be given during the period of resin therapy in order to guard against calcium and vitamin depletion.

Anticoagulant Drugs. Embolic occlusion of an artery in the pulmonary or systemic circulation is a common complication of congestive heart failure. Emboli to systemic arteries arise from thrombi in the left atrium or its appendage in patients who have auricular fibrillation or mitral valve disease, or from mural thrombi in the left ventricle when congestive failure occurs as a complication of acute myocardial infarction. Pulmonary emboli, on the other hand, originate

much more frequently from areas of phlebothrombosis in the lower extremities than from the right auricle or ventricle.

There is evidence[6] that the incidence of thrombo-embolic accidents in cardiac decompensation can be reduced significantly by the administration of anticoagulant drugs. It is our opinion, therefore, that Dicumarol® should be employed in all cases of severe failure, in all elderly persons, and in those who have decompensation with auricular fibrillation, auricular flutter, mitral valve disease or recent myocardial infarction. The drug should not be used, however, unless facilities are available for accurate measurement of the prothrombin time of the blood, and should not be given to patients who have hepatic insufficiency or a blood dyscrasia with hemorrhagic tendencies.

Morphine and Sedatives. Persons suffering from congestive failure of moderate or severe degree frequently have had no restful sleep for many nights, and this contributes importantly to their exhaustion and apprehension. In all such cases, morphine should be administered either when the patient is first seen or in the evening of that day. In severe failure, the use of morphine may be necessary on the following two or three nights, but after this, milder preparations such as one of the barbiturates, usually suffice. Mental as well as physical rest is important, and in restless, worried, or emotionally tense individuals, a relaxing sedative, such as a small dose of phenobarbital, is advisable two or three times a day during the early part of treatment.

Oxygen Therapy. The use of oxygen is unnecessary in the great majority of patients who have congestive heart failure. When moderate or severe cyanosis is present, however, or when dyspnea persists with the patient well elevated in bed, oxygen often has a decidedly beneficial effect. Oxygen therapy also is of value in combating the dyspnea and anoxia of certain complications of myocardial failure, such as pulmonary embolism, acute pulmonary edema, and pneumonia.

Venesection, Thoracentesis and Abdominal Paracentesis. In myocardial failure of the combined right and left ventricular type, the peripheral venous pressure is increased approximately in proportion to the degree of decompensation. When failure is severe, the jugular veins often are engorged to the angle of the jaw with the patient sitting upright. Venesection should be performed in such instances with the removal of 250 cc. to 500 cc. of blood, and the same procedure should be carried out in less advanced cases whenever digitalis therapy and the other measures mentioned previously fail to produce a satisfactory response. Venesection directly reduces venous congestion and diminishes the degree of dilatation of the heart. In favorable cases, the venous pressure remains low after having been reduced by the removal of blood, but in unfavorable situations peripheral venous congestion promptly returns.

Severe congestive failure often is attended by the accumulation of large amounts of fluid in one or both sides of the thorax. The resultant compression of the lungs further reduces the already diminished vital capacity and by so doing increases the degree of dyspnea. Whenever extensive pleural effusion is

present, therefore, the fluid should be removed as completely as possible by prompt thoracentesis.

Although ascites is a not infrequent complication of advanced decompensation, the amount of fluid seldom is sufficient to embarrass respiration seriously or add importantly to the patient's distress. Occasionally, however, and especially in rheumatic heart disease with mitral stenosis and tricuspid insufficiency, fluid accumulates to such a degree that the abdomen becomes greatly distended and the diaphragm markedly elevated. Removal of the fluid in such a circumstance often gives striking relief from dyspnea.

Estimation of Clinical Progress. There are a number of guides which can be used in estimating the response to treatment of congestive heart failure. Of these, the most important are relief from such symptoms as dyspnea, cough and malaise, the occurrence of diuresis, disappearance of clinical edema, clearing of the evidence of passive congestion in the lungs and liver, improvement in the vital capacity of the lungs, return of the peripheral venous pressure to normal, control of the ventricular rate when auricular fibrillation is present, and the course of the weight curve. It must be remembered that a considerably increased volume of extracellular fluid may still remain in the body after all apparent edema has disappeared. Convalescence cannot be considered satisfactory until this subclinical edema also has been eliminated. This is the reason why Gold[3] places such emphasis on the patient's weight curve and is the main consideration for recommending the use of mercurial diuretics at whatever intervals and for whatever length of time are necessary to maintain the minimal weight and a relatively constant output of urine.

In conclusion, although the majority of persons who have had congestive heart failure eventually die of a recurrence of the condition or of some other complication of the underlying heart disease, the treatment of myocardial decompensation should not be a matter of pessimism. Management according to the principles which have been outlined will restore many patients to a useful and self-supporting state for long periods of time and will contribute greatly to the comfort of the less fortunate ones who cannot be helped beyond a life of semi-invalidism.

Summary

(1) The essential features of the management of congestive heart failure consist of a period of rest, restriction of the sodium content of the diet, and the administration of digitalis, mercurial diuretics, and sedatives. In selected cases, cation exchange resins, anticoagulant drugs, oxygen, venesection, and the mechanical removal of fluid from the thorax or abdomen are useful adjuncts to treatment.

(2) A period of rest is necessary in every case of myocardial failure. Precautions must be taken, however, to prevent possible harmful effects of the recumbent position.

(3) The diet should contain not more than 500 mg. of sodium per 24 hours. In favorable cases, the limitation on sodium intake often can be lightened sub-

sequently, but only occasionally can the daily allowance be increased beyond 1500 mg.

(4) Every patient suffering from cardiac decompensation should be completely digitalized, and with few exceptions the digitalized state should be maintained permanently. For oral use, the purified glycosides have no special advantage over whole digitalis leaf. Intravenous administration of digitalis preparations is necessary only in true cardiac emergencies.

(5) Mercurial diuretics by intramuscular injection are indicated in every case of congestive failure. They usually are given daily in the early part of treatment. Excessive diuresis should be avoided, and close attention should be paid to the temperature chart for the first evidence of developing hypersensitivity.

(6) Cation exchange resins are definitely not a complete substitute for sodium restriction in the diet, but they are of value in certain selected situations.

(7) The incidence of thrombo-embolic complications in myocardial failure can be reduced by the administration of Dicumarol.(TR) Anticoagulant therapy should be employed in all cases of severe failure, in all elderly patients, and in those who have decompensation with auricular fibrillation, auricular flutter, mitral valve disease or recent myocardial infarction.

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ATLAS-AXIS DISLOCATION FOLLOWING CERVICAL ADENITIS

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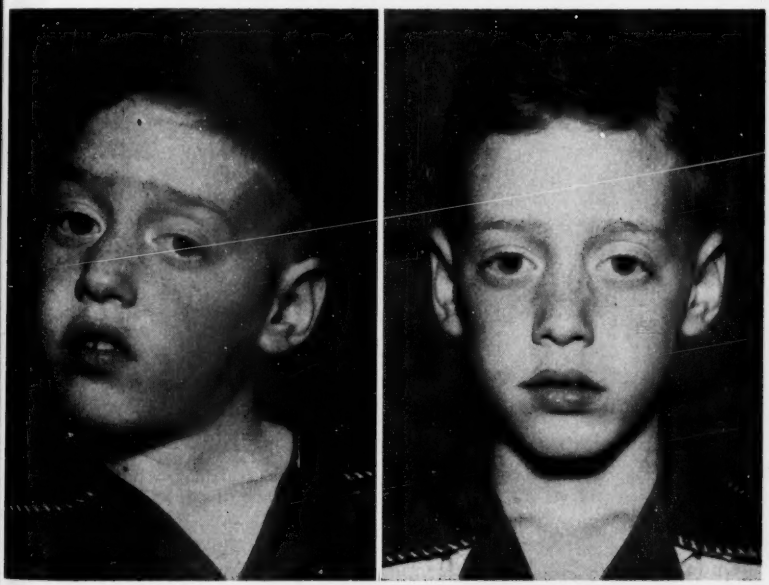
ROTARY dislocation of the atlas on the axis in association with infections about the head and neck and without known trauma is a syndrome which is seldom described. The rarity of the lesion is more apparent than real and is related to a general lack of familiarity with this syndrome on the part of the physicians. The condition was described as early as 1908.[1] The diagnosis is easily established and treatment is simple.

Anatomically, there is a forward rotary dislocation of the atlas on the axis. The articular facet on one side or the other of the atlas slips forward and downward on its opposing member on the axis and locks into position. The motion is a rotary one on the dens and requires relaxation of the various ligaments supporting the atlanto-axial articulation. There is no apparent fracture in the dens or tearing of the transverse ligament.

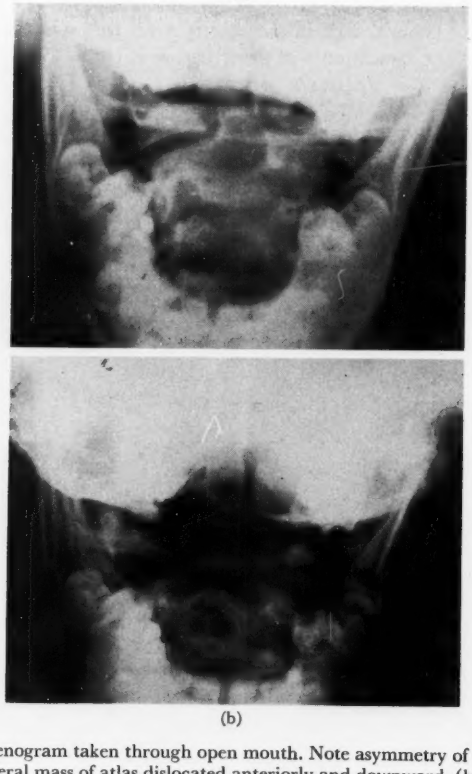


(a) (b)

FIG. 1. (a) Patient on admission. Torticollis with chin toward right shoulder. (b) Patient subsequent to head traction. Complete recovery.

Clinically, this syndrome is most often found in children of either sex between the ages of 5 and 12.[2] In our experience, it is most frequently seen following painful cervical adenitis. However, it has also been described following acute rheumatic fever, scarlet fever, mastoiditis, tonsillitis, tonsillectomy and nasopharyngitis.[3,4,5] The child apparently holds his head to one side to relieve the pain of a cervical adenitis and, after a variable period of time, he is unable to straighten it. When the syndrome develops following such an episode, the presenting problem is one of painful torticollis. Frequently all signs of the initial adenitis have disappeared.

(a)



(b)

FIG. 2. (a) Roentgenogram taken through open mouth. Note asymmetry of transverse process of atlas and left lateral mass of atlas dislocated anteriorly and downward. (b) Roentgenogram after 4 days of head traction.

On examination, the head is seen to be in the position of classical torticollis. The chin is drawn in and turned toward the side opposite the dislocation. The head is forward with the occiput tipped toward the side of the dislocation. The patient often supports his head with his hands. On palpation, there may be

some tenderness at the base of the occiput. The spinous process of the axis may be displaced laterally to the midline away from the side of the dislocation. There is usually no spasm of the sterno-cleido-mastoid muscles. There is some limitation in opening the mouth, and the size of the nasopharynx may appear to be reduced. On palpation of the pharynx just above the posterior border of the soft palate an unusual prominence can be felt which is the displaced lateral mass of the atlas. There is considerable limitation of rotation of the head. Attempted rotation is painful and can be accomplished only by rotating the lower cervical vertebrae and the upper trunk. Abnormal neurologic signs resulting from pressure on the cord by the dens are rare but have been described.[2]

The diagnosis can be established definitely by roentgenograms of the cervical spine. A lateral view will demonstrate forward dislocation of the lateral mass of the atlas. The best views, however, are obtained through the open mouth. Evident asymmetry of the lateral processes of the atlas and the axis may be observed. There is also narrowing of the joint space between the atlas and the axis in the side of the dislocation.

The most satisfactory treatment of nontraumatic dislocation of the atlas on the axis is by head traction. Reduction by manipulation under anesthesia is not advised. The patient is placed on his back with head in a slightly hyperextended position. The use of a mattress shorter than the bed facilitates hyperextention of the head. Traction is applied through a head halter running over a pulley at the head of the bed with appropriate weights attached. Countertraction is obtained by elevating the head of the bed. Traction is maintained until good reduction can be observed by repeated roentgenograms. This may require from a few days to a few weeks. When good reduction has been obtained, the head is maintained in position with a Taylor collar for 1 or 2 months. Recurrences are rare.

The exact pathogenesis of this lesion is unknown. Various theories have been proposed such as metastatic effusion into the joint spaces,[1] hyperemia and decalcification of the ligamentous attachments,[6,7] spasm and contraction of the prevertebral muscles,[4] or a combination of all of these factors.[8] The following sequence of events probably occurs:

1. Pain in the region of the upper neck causes voluntary splinting in the position of torticollis.

2. The ligamentous structures are weakened by decalcification of their bony attachments as a result of hyperemia accompanying infection. The vascularity of growing bones may explain the prevalence of this syndrome in the younger age groups.

3. Effusion into the joint spaces may be an added factor in weakening the ligaments.

4. Forward displacement occurs since the weight of the head is normally forward of its center of gravity[3] and the normal inclination of the lateral articular facets is downward, outward and forward.

5. The displaced atlas is locked into position by spasm and contraction of the prevertebral muscles.

Report of a Case

A 7 year old white boy was first seen at the Cleveland Clinic on April 24, 1952, complaining of a "twisted neck." Six weeks previously, he had experienced a sore throat and painful cervical lymph glands. He was treated over a period of 2 to 3 weeks with penicillin and a sulfonamide by a pediatrician and seen in consultation by an otolarynoglogist. The cervical adenitis had responded to treatment but torticollis had appeared and had persisted.

On examination, the child was observed to be holding his head in the position of torticollis (fig. 1a); the chin was toward the right shoulder and he was supporting his head with his hands. The cervical lymph glands were not tender. Rotary motion of the head was impossible without rotation of the upper trunk. Slight tenderness was noted below the occiput. The pharynx was not palpated. No abnormal neurologic signs were present and the remainder of the physical examination was normal. Routine examination of the blood and urine showed no abnormalities.

A dislocation of the atlas on the axis was suspected and appropriate x-rays were obtained. Severe asymmetry was evident in the joint spaces between the atlas and the axis. The joint space was narrower on the left than on the right. The left lateral mass of the atlas was seen to be dislocated anteriorly with regard to the axis (fig. 2a).

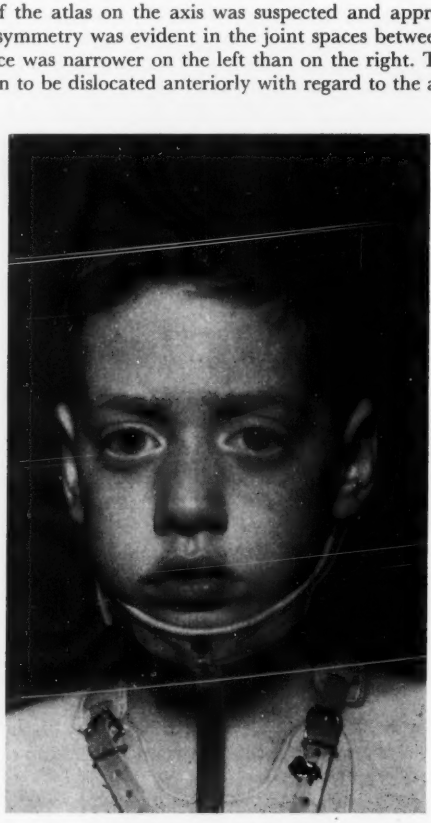


FIG. 3. Taylor brace supporting the head following reduction of dislocation.

Traction was applied by means of a head halter with an 8 pound weight. Complete reduction was demonstrated in 4 days (fig. 2b). Traction was maintained for 10 days and then replaced with a Thomas collar (fig. 3). At the end of 6 weeks, this was removed and the child has remained well (fig. 1b).

Summary

The syndrome of nontraumatic dislocation of the atlas on the axis is described. This condition occurs following infections about the upper neck and it is thought to be more common than generally realized. The diagnosis is easily established when considered, and treatment is by simple head traction followed by support of the head over a period of a few months.

Acknowledgment: This patient was under the orthopedic supervision of Dr. A. W. Humphries of the Cleveland Clinic to whom we offer our sincere thanks.

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CARCINOMA OF THE COLON IN CHRONIC ULCERATIVE COLITIS

Report of Two Five-Year Survivals

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IT is generally understood that carcinomas of the colon arising in the course of ulcerative colitis are highly malignant and invasive,[1,2] metastasize early and have a short survival period following resection. The following 2 cases are reported because the patients are alive and well, without evidence of recurrent neoplasm for 5 years.

Case Reports

Case 1. A 56 year old white man was seen for the first time at the Clinic on January 21, 1948. He had suffered from a mild chronic ulcerative colitis involving the entire colon and rectum for a period of 10 years. Frequent roentgenograms were taken of the colon and proctoscopic examinations were made during this interval. At no time had his symptoms been severe enough to warrant surgical intervention. During the preceding year he had noted frequent bleeding from the rectum, after which he submitted to examinations at closer intervals. Six months prior to admission to the hospital, several ulcerating lesions were found in the rectum. Repeated biopsies revealed adenocarcinoma. The patient was admitted to the hospital on February 10, 1948, at which time abdominoperineal resection was performed. His convalescence was uneventful.

Pathology: The open rectum and sigmoid colon revealed considerable thickening of the walls with loss of the usual mucosal folds. The mucosa was finely granular and manifested all the characteristics of chronic ulcerative colitis. Eight cm. above the dentate line the mucosal surface presented 5 rounded elevations with finely granular surfaces, the largest of which was 1.5 cm. in diameter and raised above the mucosa for approximately 1 cm. These areas were firm and sections revealed them to be papillary adenomata of the flat type with adenocarcinoma extending through the muscularis mucosa into the submucosa but without penetration of the muscularis. Eight lymph nodes were recovered from the mesentery of the rectum and sigmoid colon and none were found to be involved with secondary neoplasm.

At the present time this patient has mild symptoms of ulcerative colitis, but he has refused to undergo colectomy with ileostomy. We feel that he will in all probability develop another carcinoma in the colon, should he live long enough. He has now survived 5 years since the carcinoma was detected.

Case 2. A 46 year old white woman was seen at the Clinic for the first time on April 11, 1947. She was known to have had chronic ulcerative colitis involving the entire colon and rectum for a period of 5 years. Roentgenograms taken elsewhere were said to have revealed mild ulcerative colitis. Eight months prior to admission laparotomy was performed by the referring physician and a cecostomy was made to divert the fecal stream. After this a gain was apparent in weight and strength. However, 4 months before admission to the Cleveland Clinic Hospital she began to experience lower abdominal cramps, particularly on the left side, with an increased urge to move her bowels through the rectum and with the passage of small amounts of blood, mucus, and pus. Films of the colon made at home in July, 1946, were said to have revealed segmental ulcerative colitis of the sigmoid colon. After admission to the Clinic hospital x-rays made of the colon were reported as showing evidence of mild chronic ulcerative colitis throughout. Proctosigmoidoscopic examination revealed minimal changes in the mucosa, suggesting ulcerative colitis. Because of the severity of the symptoms, a right colectomy with end ileostomy was performed on April 23, 1947.

The right side of the colon revealed a typical nonspecific chronic ulcerative colitis with thickened and edematous mucosa. Small pinpoint ulcers were noted along the sides of the mesenteric attachment. During the patient's convalescent period there was copious amount of blood from the rectum and the left-sided cramps were severe and continuous. Three months later she was readmitted for removal of the left colon. She stated that during the interim she had noted frequent passage of blood and mucous from the rectum and experienced a nagging pain in the left side of the abdomen, The latter persisted most of the time. On July 15, 1947, left colectomy was performed and, as the colon was rotated from the abdomen, a small papillary carcinoma was palpated in the upper sigmoid colon. Abdominoperineal resection was performed 3 months later. During the period between left colectomy and this procedure, the patient made a rapid recovery, with accompanying gain in weight, and there were no longer any symptoms to suggest either ulcerative colitis or carcinoma. The adenocarcinoma of the sigmoid colon was of the mucinous type, with but slight extension into the pericolic fat. One of 4 lymph nodes recovered from the mesentery was involved with secondary neoplasm. Sections of the colon revealed ulcerative colitis in the inactive phase. The patient was last seen in July, 1952, and has survived 5 years since the resection was performed. She is well and without evidence of metastases. We consider most of her symptoms to have been due to the carcinoma rather than to the diffuse ulcerative colitis.

Discussion

The preceding 2 cases merit attention for several reasons. First, it is rare for patients with carcinoma arising in ulcerative colitis to survive 5 years. Such neoplasms are usually highly malignant, metastasizing before operation. In addition, a neoplasm may be rather difficult to detect because the symptoms and even roentgenologic changes may be attributed to an exacerbation of the colitis, as demonstrated in case 2.

Ulcerative colitis has usually preceded the development of carcinoma by a number of years; in our series[3] by an average of 16 years. The first patient reported here had ulcerative colitis for 10 years and the other for only 5 years. A 5 year history of colitis prior to the development of malignancy is relatively short and unusual. Neither patient had polyps nor pseudopolyps. While many

of the neoplasms of the colon in patients with ulcerative colitis appear to be associated with pseudopolyposis, some may develop malignancy without them. Absence of pseudopolyp or polyp, therefore, is no indication that the patient will not develop carcinoma of the colon. Although the pathogenesis of the neoplasm is believed to be chronic inflammation and irritation resulting in hyperplasia, proliferation, and finally carcinoma, the exact mechanism is unknown. However, it seems definite that chronic ulcerative colitis has a prefatory relationship to colonic cancer.

More recent reports essentially agree that the incidence of carcinoma is higher in patients with ulcerative colitis than in normal persons. Bargen[4] has repeatedly reported a series of cases in which the incidence of carcinoma was greater than would normally be expected. He found the incidence to be 3.2 per cent in a series of 874 patients with ulcerative colitis. Jackman et al.[5] found six instances of malignancy in 95 cases of ulcerative colitis in children. Multiple carcinomas of the colon have been reported in 7 of 27 patients by Bargen and Dixon[6] and in 8 of 26 cases of ulcerative colitis by Sauer and Bargen.[7] We[3] found, from 1945 through 1949, that 3.8 per cent of our patients with ulcerative colitis developed cancer. The actual incidence in these patients probably is higher than the quoted figures and one needs only to follow them long enough. Since the symptoms of the two conditions can be so similar, a physician may believe that a patient has died from an exascerbation of ulcerative colitis, while actually the cause of death may have been an undetected neoplasm of the colon; only total colectomy or postmortem examination would disclose such a neoplasm. We agree with Cattell and Boehme,[8] it would seem that as the percentage of operations increases, particularly colectomy, the number of carcinomas found would increase also. We must be conscious of the fact that carcinoma of the colon is more frequent in patients with ulcerative colitis, that the carcinoma is highly malignant, and that the symptoms of the carcinoma may simulate those of the colitis.

The question arises: What patients with ulcerative colitis are most likely to develop carcinoma? Certainly carcinoma is not apt to develop in a patient whose infection is limited to the rectum and whose disease promptly subsides on medical treatment. The development of carcinoma is dependent on three factors: the degree of infection or inflammation, the amount of colon involved, and the duration of the disease. The more severe the infection, the more extensive the involvement of the colon; and the longer the colitis has existed, the more likely that the patient will develop carcinoma. Most of the patients we have seen with carcinoma arising in ulcerative colitis have had severe involvement, usually of the entire colon. Likewise, most have had chronic ulcerative colitis for a considerable time, an average of 16 years in our series.[3]

Because of the highly malignant nature of the neoplasm in these patients, by the time such a lesion can be demonstrated by roentgenographic examination, the patient is usually incurable. Consequently, it is of little value to obtain yearly barium enema examinations in order to detect such a lesion at an early stage. The only way to treat carcinoma of the colon in patients with ulcerative

colitis is to prevent the neoplasm from developing by prophylactic colectomy in those patients most likely to develop malignancy. With simultaneous ileostomy and subtotal colectomy,[9] the patient requires only 1 operation, or, at the most, if abdominoperineal resection is done subsequently, only 2 operations. The mortality of simultaneous ileostomy and subtotal colectomy in nontoxic cases since 1948 at the Cleveland Clinic has been no deaths in 50 operations. It can be seen that the operative treatment has greatly improved and the operative mortality has been reduced to the extent that the hazard of surgery is no longer a detriment.

Many patients with ulcerative colitis respond to medical treatment with healing of the ulcers and without evidence of recurrence. This is particularly true of those patients with the disease limited to the rectum and sigmoid colon. One is not concerned about these patients having a high incidence of carcinoma of the colon, and it is not our purpose to urge colectomy in every patient with ulcerative colitis. At the Cleveland Clinic[10] we have operated on only 13 per cent of these patients. We believe that practically every patient should have a thorough trial on medical treatment before surgery is recommended.

Because of the increased incidence of highly malignant neoplasms in patients with ulcerative colitis, we believe that serious consideration of subtotal colectomy is indicated under the following conditions:

1. Chronic forms of colitis that have not responded to medical treatment, and have been present for a considerable length of time. Most of these patients have involvement of the entire colon. The more severe, protracted and chronic the disease, the more urgent the operation.

2. The presence of polyps or pseudopolyps. While carcinoma may develop without polyps, as in the two cases presented, neoplasm develops more frequently in those patients with ulcerative colitis who do have polyps. Colectomy is indicated in any patient with ulcerative colitis and pseudopolyposis.

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BERYLLIOSIS

Summary and Survey of all Clinical Types in Ten Year Period

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THE metal beryllium, in addition to exhibiting unusual chemometallurgic properties, has in the last decade brought to the attention of the medical world its puzzling physiologic and pathologic effects in man. Up to the present the largest number of cases of beryllium intoxication have occurred in plants engaged in the extraction and processing of beryllium and in the manufacture of fluorescent lamps.[1] The least number of cases have been reported from workers engaged in the salvage of fluorescent lamps, in sign tube manufacture, in laboratory research, in the manufacture of ceramic containing beryllium, in the manufacture of beryllium alloys, and in the working of beryllium metal. No known beryllium cases have been reported in the mining, shipping and handling of beryl ore.

Recognition of occupational hazards involving either the derma and/or the respiratory tract came in the early years of the beryllium extraction and processing industry. Since 1940 the authors have observed and treated 461 cases of the various types of beryllium poisoning. Table 1 is a summary of the incidence, mortality and causative compound of the acute manifestations encountered in plants A, B and C. Dermal and ocular manifestations were evident in 202 cases; minor and major respiratory tract involvement occurred in 229 persons. This survey also includes 2 dermal and 31 pulmonary cases of the chronic form of the disease. Many of the cases included have been reported in previous publications.[2,3,4]

The data in this survey are presented to bring to the attention of the toxicologist, the industrial hygienist, and the many other interested clinicians the progress and present status of beryllium intoxication as studied and evaluated by the authors in the last decade. This study has been made possible by the fact that during the last 15 years the major concentration of plants (4) and employees (2200) engaged in beryllium extraction and processing have been located in this area in Ohio.

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A brief resume of the basic operations and uses of beryllium will aid in a clearer comprehension of the factors involved and the magnitude of the toxicologic problems encountered in the occupational diseases associated with this limited but rather vitally important chemical industry.

Elemental beryllium is a light, greyish, brittle and stable metal. Its atomic number is 4 and 1 natural isotope has been established; 3 artificial ones have been developed. It was first identified by Nicholas Vauquelin in 1797 while proving the chemical identity of beryl, emerald and aquamarine. The industrial development of the element has occurred in the last 2 decades.

Ores containing beryllium have not been found in large compact bodies. About 40 classified minerals containing beryllium are known but only 1, beryl (beryllium aluminum silicate) with an average yield of 12.5 per cent of the oxide or 4 per cent of the metal, is of industrial significance. The majority of the ore processed in this country is imported from Brazil.

At the present time the beryllium producers are concentrating their production efforts on the metal, the oxide and the alloys. The extraction methods vary, but the basic concept is to alter the natural beryllium oxide so that it can be extracted from the mineral matrix in pure form. In order to attain this, any one or combination of 2 economically sound basic methods are being used which entail the initial reduction of the ore in furnaces, followed by the use of sulfuric and/or fluoric acids to obtain soluble salts. Intermediate operations may utilize alkaline materials such as ammonium hydroxide. The present rapid research being done on production methods frequently alters the materials and methods used in the various operations so that a standard procedure of today may be altered or discarded tomorrow.

Beryllium metal is lighter than aluminum, is extremely penetrable to x-ray, is an excellent transmitter of sound and an excellent source of neutrons. It is mainly used for windows of x-ray tubes and in nuclear physics development.

Beryllium copper alloy is noted for its unusual resistance to fatigue and impact, for its corrosion resistance, for its freedom from elastic drift and for its high electrical and thermal conductivity properties. Present use includes specialized machine and equipment parts, special springs and safety tools.

Beryllium oxide has a melting point of 2570 C., is an excellent insulator at high temperatures, has unusual resistance to thermal shock plus a high thermal conductivity. Some of the past and current uses of the oxide include: high temperature crucibles and shapes, phosphors in fluorescent lights and neon signs, radiation shields, lining in coreless induction furnaces, cathode heating elements in radio tubes, ceramics and vacuum tube "getters."

Any survey of a toxicologic problem, such as that of beryllium, must not forego the progress in therapy. Foremost in this category one must stress the more important preventative features in the beryllium processing plants and their surrounding environments. These hygienic preventative measures are most important in view of lack of effective or specific therapy, especially with reference to the chronic pulmonary disease. In consideration of these accepted

facts certain engineering and medical hygienic standards have been adopted in order to protect those who are exposed to beryllium or its compounds.

Upon recommendations advanced by Eisenbud and associates[5] and the Atomic Energy Commission, the extracting plants have adopted engineering devices to control the atmospheric concentration of beryllium in order that the plant working environment will not exceed the daily average permissible concentration of 2 micrograms per cubic meter; that no transient concentration will exceed 25 micrograms per cu. M. and that the vicinity of any plant subject to atmospheric pollution by beryllium not exceed a maximum permissible monthly average concentration of .01 microgram per cu. M. Although these figures are tentative and arbitrary, they have added effectiveness since their initial application in reduction of the incidence of acute and chronic disease.

To further maintain a continued high standard of protection for the workers, certain medical procedures and basic control methods have been instituted in a well organized medical department.[6,7]

The present and very effective integrated medical safety and industrial hygiene program adopted in the extraction plants includes rigid pre-employment screening with disqualifications based on certain physical abnormalities or history of pre-existing diseases considered incompatible with the industry. To achieve continued and maximum effective prophylaxis, new employees are instructed in a rigid standard program of health and safety education. All employees are required to have weekly examinations including pulmonary roentgenograms. During the last 4 years this program, mainly under the direction and supervision of one of our co-workers,* has been most effective in the remarkable reduction of the incidence and total elimination of mortality (table 1) with most of the reported cases having been traced to major mechanical breakdowns, personal failures or experimental procedures. Furthermore, these medical and engineering safeguards have aided considerably in the maintenance of better health, better labor management relationship, and a decrease in labor turnover with a concomitant decrease in production costs.

Some of the manifestations of beryllium intoxications have been reproduced by animal experimentation.[8,9] Sufficient evidence has been obtained both clinically and experimentally that beryllium, per se and by its bond with other elements and radicals, is capable of expressing various forms of toxicity in certain environmental concentrations and probably in the presence of certain altered physiologic conditions. The most recent epidemiologic investigations suggest that the beryllium ion is the sensitizing allergen in both the dermal and pulmonary syndromes.[10,11] This aspect is being investigated.

In the various groups of cases studied in the present survey we have emphasized the importance of the urinary excretion of the element and the beryllium content of the necropsied tissues. The spectographic and the fluorimetric, 2 sensitive biochemical analytical technics, were employed by 2 lab-

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oratories* in obtaining the recorded tabulated data of our survey. The value and significance of beryllium determinations in the urine of persons exposed to the element, with or without toxic manifestations, is adequately covered by Dutra and co-workers,[12] and Klemperer and associates.[13] Generally our data are in agreement with the findings and conclusions of the preceding investigators. Table 2 is the survey data on 10 persons having undergone varying periods of exposure without specific occupational disease, all showing evidence of beryllium excretion in varying amounts; and on 2 patients having had constant exposure to insoluble BeO for 5 years who still showed appreciable excretion despite 5 years' removal from contact.

In the course of the present survey we have been able to secure tissue at autopsies of 2 patients having recovered from major respiratory beryllium intoxication with subsequent death from other causes. To the knowledge of the authors no tissue analyses of similar cases have been reported in the literature. Brief case histories are given along with pulmonary roentgenogram plus table 3 tabulating the tissue analysis and beryllium urine determination in case 2 taken during the survey of 1950. It is evident that the analytical figures of these 2 cases strongly support the fact that the quantity of beryllium in the tissues or the quantity excreted in urine after years of freedom from contact with beryllium is merely indicative of previous exposure to the element and not necessarily specific disease. Case histories and findings are as follows:

Case 1. A man 50 years old at time of death, was first employed in a beryllium extraction plant on September 22, 1944, as a mixer in the beryllium copper department and a furnace operator's helper in the beryl furnace department. Exposure was insidious over a period of 64 days and mainly to the dusts of beryllium oxide, graphite and fumes of reduced silicates including $BeSO_4$ and BeF_2. The patient developed an acute chemical pneumonitis on November 24, 1944 (fig. 1, case 1). Clinical recovery, as shown roentgenographically, was apparently complete by March 26, 1945 (fig. 2).

In September 1946 he noticed a severe anorexia, weight loss and a productive cough. Symptoms became progressively aggravated and the patient died in a veterans' hospital on February 14, 1947. The final diagnosis was generalized carcinomatosis with many pulmonary metastases (fig. 3). The beryllium contents of certain autopsied tissues are reported in table 3.

Case 2. A man, 36 years of age at time of his death in 1951, was first employed as a furnace operator in the crystallizing department on January 20, 1942. He was exposed to fumes and mists of soluble salts of beryllium, mainly BeF_2, in varying atmospheric concentrations. He left the industry in the fall of 1946 and had no further exposure to beryllium.

During his employment in the beryllium extraction industry he developed 2 attacks of acute chemical tracheobronchitis due to BeF_2 during the following periods: March 3 to March 12, 1943, and September 3 to September 21, 1943. Recovery was complete in both instances.

The patient was examined for the survey on August 1, 1950, and found to be in excellent physical condition with vital capacity of 5.6 L. or 120 per cent of normal. Roentgenograms taken on July 21, 1950, revealed normal lung findings except for some mild interstitial fibrosis of the right lung (fig. 4, case 2). Urine determination of 24 hour specimen on August 1, 1950, revealed the presence of 0.6 micrograms per L.

The Kettering Laboratory of Applied Physiology and the Atomic Energy Commission Laboratory.

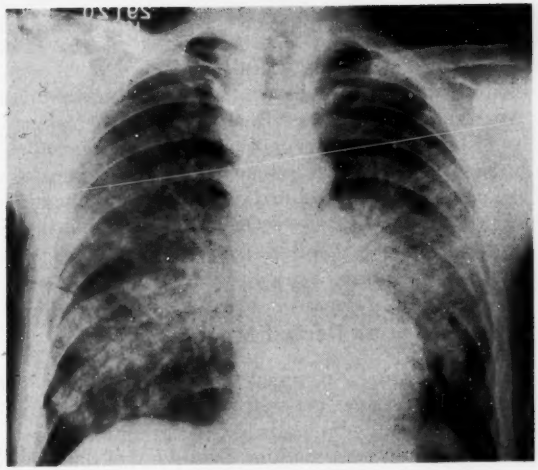

FIG. 1, Case 1. Pneumonitis involving hilar and central pulmonary areas 25 days following onset of illness (12-9-44).

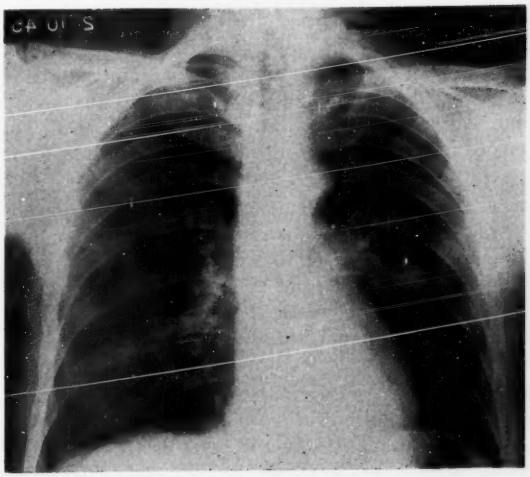

FIG. 2, Case 1. Pneumonitis cleared except for slight hilar residue. Patient fully recovered (2-10-45).

The patient died of acute carbon monoxide asphyxia on June 28, 1951, as verified at autopsy. The beryllium contents of the tissues as reported by 2 separate laboratories appear in table 3.

The preceding and ensuing data are the result of observations and experiments with workers exposed to beryllium and with certain pattern diseases due to toxicity of beryllium and/or its compounds. Important factors encountered in the survey including the present status of each person, exposure data plus analyses of urine and the autopsied tissues, are tabulated under each main heading. Present day therapy is also recorded along with a brief description of the main causative compounds, subjective symptomatology and physical and laboratory findings.

Acute Dermal Manifestations

The dermatitis was usually confined to the exposed parts of the body but in the sensitivity type became generalized. The lesions varied from diffuse papules, and vesiculopapules to macules and irregular areas of edematous lesions with or without vesicle formations. Symptoms of the majority of patients consisted of a burning sensation and pruritis of the affected parts. Usually there was a concomitant involvement of the conjunctivae and eyelids.

Up to the year 1947, due to the rapid turnover of a migratory group of employees, approximately 25 per cent of new workers exposed to the fumes, mists and dusts of the soluble salts of beryllium developed dermatitis of varied intensity depending on individual sensitivity. The subsequent hygienic engineering plant improvements, in addition to a well organized and rigid medical screening of new employees, has reduced the incidence to less than 2 per cent.

The response to treatment varied, the fluoride compound cases being most refractory, but recovery usually was complete in 7 to 14 days after removal from exposure. The present therapy consists of immediate transference from the offending agent, the use of antihistaminics and the local application of mild, soothing, antipruritic and antihistaminic ointments. The concomitant conjuctival involvement usually requires the use of soothing antibiotic ophthalmic ointments and wearing of dark glasses.

Up to the present, 209 acute dermal cases have been observed by the authors over a period of 12 years without any resulting fatalities or local residuum. The dermal manifestations were, with a few exceptions, caused by contact with the soluble forms of beryllium, principally the fluoride and the sulfate. One hundred sixty-four cases were ascribed to the fluorides while the remainder (45 cases) were due to sulfates. Undoubtedly some patients had contact with both compounds.

Sixty-three of the 209 cases were attributed to exposure to the soluble salts of beryllium in sufficient concentration to act as a primary irritant and produce an immediate contact dermatitis. In 146 cases eczematous type of dermatitis, often a severe manifestation, developed as the result of acquired sensitization attributed to longer exposure to smaller concentrations of beryllium salts. The dermatitis appeared on an average of 7 to 14 days after initial exposure.

There were 5 cases included in this dermatitis series in which major respiratory syndromes occurred. Patient 10, table 7 of the chronic berylliosis group, had acute dermatitis due to BeF_2 and patients 1, 2, 5 and 19, table 5 of the recovered pneumonitis series, also had acute dermatitis during their employment in the beryllium industry.

Prior to 1951 it was thought but not demonstrated that the eczematous form of the dermatitis was of the allergic eczematous contact-type. Of 13 patients studied by one of us,[11] 4 had had the dermatitis at one time during the past 6 years and 9 patients had the dermatitis during the period of observation. Cutaneous allergy was demonstrated by the patch test technic with high dilutions of beryllium compounds. In a series of 16 controls who had never been exposed to beryllium and/or its compounds, cutaneous hypersensitivity was produced in 8 (50 per cent).

Beryllium Ulcer—usually an acute localized manifestation due to implantation of the crystals of the soluble salts of beryllium in a pre-existing skin break. It is often a concomitant manifestation with contact dermatitis and the pathologic findings are those of a severe skin reaction to a primary irritant. Untreated lesions may persist for months. Treatment consists of curettage of the ulcer and removal of the offending beryllium salt inclusions. Healing is by second intention and usually complete from 7 to 14 days.

Acute Tracheobronchitis and Pneumonitis

Acute tracheobronchitis, as studied in our series of cases, invariably was caused by inhalation of vapors, dusts and mists of BeF_2, ammonium BeF_2, $BeSO_4$. The onset is either rapid or insidious depending upon the magnitude and duration of the exposure. Symptomatically it is characterized by productive spasmodic cough, substernal discomfort and burning, tightness of the chest, and moderate exertional dyspnea. The objective physical findings reveal normal body temperature, decreased vital capacity with varying degree of dyspnea, injection of the nasopharynx, limitation of chest expansion, and the presence of sibilant rales in the hilar and basilar areas of the lungs; clinical laboratory findings within normal limits. The pulmonary roentgenograms may show increase of bronchovascular markings.

The therapy is not specific and consists of removal from exposure, bed rest, cough sedatives, antihistaminics to relieve bronchiolar spasm, and antibiotics to prevent and control secondary invaders. Recovery is usually complete in 1 to 4 weeks.

Up to the present time 129 cases of acute tracheobronchitis have been observed and treated over a 12 year period. Sixty-two instances were due to BeF_2, 38 to $BeSO_4$, and 29 to inhalation of mixture of the soluble salts. Clinical and roentgenographic recovery was complete in all cases.

Of this entire group, 34 persons were available for the survey study with one nonoccupational death reported in table 3. The majority of the remaining group could not be contacted as this disease occurred largely in migratory

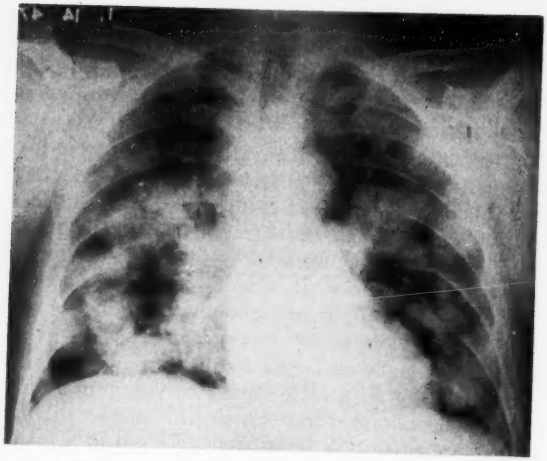

Fig. 3, Case 1. Metastatic tumor nodules scattered throughout both lung fields (1-14-47).

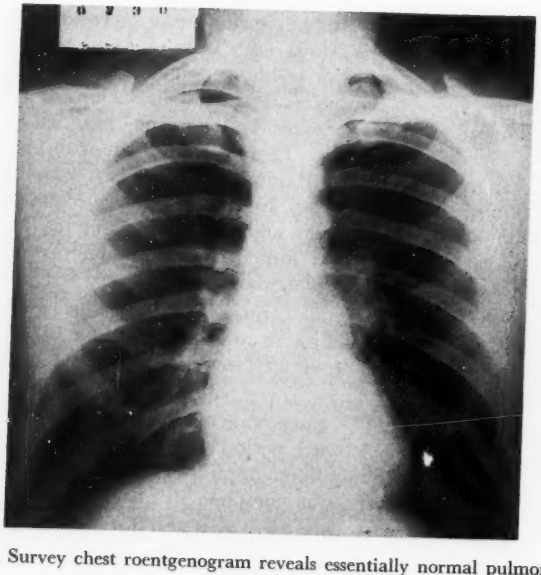

Fig. 4, Case 2. Survey chest roentgenogram reveals essentially normal pulmonary findings (7-21-50).

workers during the war years. Table 4 is a summary of the survey data of 20 of the recovered patients who had had acute tracheobronchitis; 8 persons are engaged in the same industry since recovering from their acute tracheobronchitis. One patient (case 12, table 7) who had two attacks of the disease in 1945 developed chronic berylliosis in 1947. There is also the suggestive history of acute tracheobronchitis in two other persons with chronic berylliosis (cases 8 and 11, table 7) but no confirming medical record was established by either patient.

The data in table 4 reveal the excretion of beryllium in the urine of all the recovered patients. The group still exposed in the processing plants generally show a greater excretion of the element, while in the remaining cases there is suggestive general decrease of the beryllium excreted in relation to the last date of exposure.

Acute Chemical Pneumonitis

Briefly, acute chemical pneumonitis is caused by inhalation of vapors, mists and dusts of BeF_2, $BeSO_4$, combinations of the soluble salts and BeO of high specific area prepared at relatively low calcining temperatures.

Two types have been encountered, namely the fulminating and insidious, depending upon the magnitude and duration of exposure. The symptoms of fulminating pneumonitis usually occurred approximately 72 hours after brief but massive exposures, while the insidious form manifested symptoms several weeks after prolonged exposure to lesser concentrations in the working environments.

Symptomatically it is characterized by progressive, rarely productive spasmodic cough, progressive dyspnea with tightness of the chest and substernal pain or discomfort, anorexia with ensuing weight loss, general malaise and weakness. The objective findings reveal varying degrees of decreased vital capacity with severe dyspnea, rapid pulse and acrocyanosis, hyperemia of the nasopharynx, no increase of body temperature, limited chest expansion with variegated pulmonary rales principally in the lower lobes and hilar areas. Clinical laboratory findings are within normal limits.

Pulmonary roentgenograms become positive in 1 to 3 weeks after onset of symptoms and vary with the stage and intensity of the disability. Findings in chronologic sequences are: diffuse bilateral haziness usually of the lower lung fields followed by irregular soft parenchymal infiltration and finally discrete or conglomerate nodules. Therapy is not specific and consists of hospitalization with complete rest, use of oxygen to relieve respiratory distress, antibiotics as prophylaxis against secondary infection, antihistaminics to alleviate bronchiolar spasm, digitalization in evidence of cardiac decompensation, and the recent use of cortisone and ACTH with some preliminary gratifying results.

This has been the severest manifestation of acute beryllium poisoning which has been observed and treated in 93 instances as result of exposure in the local extraction and processing plants, with 10 deaths during the last 12

years or a mortality of 10.7 per cent. Of this group 35 cases were due to BeF_2, 8 to $BeSO_4$, 17 to mixtures of the soluble salts and 33 to BeO. Clinical recovery and roentgenographic clearing was complete in all but one of the living patients reported in table 5 as case 8. No incidence of chronic berylliosis was detected in any of the cases studied in the survey.

Survey data have been obtained on 40 of the recovered and living patients having had acute pneumonitis and the results of our survey of 20 persons are listed in table 5. Five of this group have continued working with beryllium and generally show a larger urinary excretion of the element than the remaining number. Again, as in the cases of tracheobronchitis, the remaining group reveal the presence of the element in the urine; this, roughly, is in proportion to the number of years since the last exposure.

Autopsy and tissue analyses were obtained in 7 of the 10 deaths in this group and the tissue content of beryllium was considerably higher than the necropsy analyses of the chronic cases (table 6).

Chronic Pulmonary Granulomatosis

As defined by Machle,[14] chronic pulmonary granulomatosis or berylliosis is a generalized disease characterized by pulmonary insufficiency, having the major pathologic changes in the lungs, the most characteristic lesion of which is the granuloma. The outstanding feature of all cases of chronic berylliosis is a delay in onset from a few months to several years after initial exposure. The pathologic aspects of the acute pneumonitis and chronic pulmonary granulomatosis have been adequately covered in several publications and especially by Hazard,[4] Chesner[15] and Dutra.[16]

Symptomatically the disease is characterized by insidious onset with a nonproductive, spasmodic, paroxysmal, persistent cough; chills and fever; anorexia, with asthenia and definite loss of weight; progressive exertional dyspnea with substernal pressure and bizarre thoracic pains. The objective findings are: varying exertional dyspnea; increased pulse rate; decreased vital capacity; "watch-glass" fingernails or clubbing of fingers; acrocyanosis; decreased thoracic expansion and presence of crackling rales throughout both lung fields in the advanced stages of the disease. Routine and special laboratory procedures have failed to reveal any specific common abnormal findings. Serial cardiopulmonary roentgenograms reveal a transition from a generalized "ground glass" or granulation of the parenchyma in the early stages of the disease to the late phases of nodulations, emphysematous changes and cor pulmonale.

The treatment consists of restriction of physical activity below that permitted by the vital capacity; use of antihistaminics to relieve bronchiolar spasm; oxygen for respiratory distress; antibiotics to control any acute respiratory infection; digitalis for cardiac decompensation; cortisone and ACTH in the aggravated state of the disease and in cases showing progression of symptoms. The use of the two latter products in treatment of chronic beryllium

poisoning was reported in detail at a symposium at the Massachusetts General Hospital in December 1950. [17,18]

This chronic type of pulmonary disease first manifested itself in a resident in the immediate vicinity of one of the beryllium extraction plants in January 1944. To date we have observed and treated a total of 31 persons with rather typical clinical and pulmonary roentgenographic patterns of the chronic disease. All gave histories of occupational or nonoccupational exposure to beryllium or its compounds in varying degrees of atmospheric concentration. The nonoccupational cases numbered 12 with 6 deaths; 8 patients in this group were exposed to atmospheric pollution within a radius of less than three quarters of a mile from the beryllium extraction plant while 4 gave definite histories of exposure to the household concentration produced by soiled work clothing of beryllium workers.

Of cases resulting from occupational exposure in the various plants extracting or utilizing beryllium or its compounds, 7 with 1 resultant death occurred in 3 plants engaged in beryllium extraction from the ore, production of the Be alloys and Be research. The total employment of the 3 plants in question was approximately 2200 persons for the period from 1940 to 1952. The remaining cases numbering 12 were from other areas of the country and in plants with occupational exposures to phosphors of beryllium.

The present status of this group is that approximately 50 per cent are static or showing some improvement, 15 per cent are showing progressive regression and, at this time, the mortality is approximately 35 per cent. Of the 8 deaths in this category, 5 autopsies were obtained and the beryllium analyses of the tissues are reported plus the beryllium findings of the 24 hour urine analyses in 2 cases (table 6). Disregarding the inconsistency and disparity in the tissue findings of the various laboratories, it accentuates the fact that beryllium was present in the tissues in all 5 instances. The absence of beryllium in the single 24 hour specimen of urine in 2 cases may or may not be of significance as to possible tissue fixation of the element, temporary retention, or degree of sensitivity of the analytical method utilized.

Table 7 is the survey record of 12 living persons representing various types of exposure and present status. Every recorded urine analysis reveals the presence of beryllium; especially is this consistent by the fluorimetric method of analysis utilized at present by one of the laboratories.

Chronic Beryllium Granuloma is a subcutaneous lesion usually the result of implantation of beryllium phosphor (zinc beryllium silicate) in a skin laceration or puncture produced by a broken fluorescent tube. Lesions are always localized or self limited and usually appear 1 to 4 months after implantation of the phosphor; they are characterized by formation of a subcutaneous nodule which may eventually develop central necrosis and subsequent surface drainage. The treatment is thorough cleansing and debridement of fresh wounds and adequate wide surgical excision of the existing granulomas.

Two cases have been observed and the patients treated by the authors; 1 was previously reported in 1950.[19] The microscopic pathologic change in

both instances is identical with the pulmonary granulomas described in chronic pulmonary berylliosis. Beryllium was found in the involved tissues.

Summary

During the period of 1940 to 1952, the authors have observed and treated a total of 431 patients with various manifestations of acute beryllium intoxication. There were 10 fatalities in the pneumonitis group.

In recent years the incidence of cutaneous berylliosis among workers in the beryllium industry has been reduced from 25 per cent to 2 per cent and the respiratory syndromes almost to zero by engineering and medical hygienic preventive measures.

The eczematous type of dermatitis is caused by allergic sensitivity to beryllium compounds.

Clinical and laboratory data were obtained on more than 75 cases of recovered tracheobronchitis and pneumonitis and detailed tabulation is presented in 20 cases in each group.

From 1944 to 1952, 30 cases of the chronic dermal and pulmonary forms of beryllium have been observed and the patients treated, with 8 resultant deaths. Exposure factors, urine analyses for beryllium and other pertinent data are recorded for this group, plus tissue analyses for the element in 5 autopsied cases.

Significant data are presented of beryllium findings in the necropsied tissue of 2 patients who recovered from major acute respiratory manifestations, but died later from other causes years after removal from exposure.

The presence of beryllium in body tissue and urine is indicative of past or recent exposure to beryllium. The amount detected by present analytical methods does not bear any relationship to existence or severity of specific disease process.

Beryllium remains in body tissues and is excreted for a period of many years after removal from exposure without evidence of beryllium poisoning.

In our survey there is some evidence of proportional decrease of excretion of beryllium with increase of time from last exposure.

No persons included in the survey of recovered cases of acute pneumonitis have developed the chronic or delayed form of berylliosis.

Of the 8 instances of chronic berylliosis of occupational origin, 1 patient had a medically established diagnosis of acute tracheobronchitis while 4 others gave histories suggestive of acute tracheobronchitis during brief occupational exposures to beryllium.

The integrated medical, safety, and industrial hygiene program has been largely responsible for the phenomenal decrease in incidence of beryllium poisoning and total elimination of deaths in the local extraction plants. Therapy is mainly symptomatic and conservative, with recent evidence of therapeutic encouragement from the use of ACTH and cortisone in both the chronic and acute manifestations.

The authors express appreciation for the material assistance given by Dr. John Zielinski.

Summary of Annual Incidence and Time Lost Classified According to Probable Causative Compounds (Plants A, B and C)

Summary of Annual Incidence and Time Lost Classified According to Probable Causative Compounds (Plants A, B and C)

Year	Pneumonitis				Tracheobronchitis				Dermatitis				
									Contact Hypersensitivity		Contact Only		Lost Time Days
	BeF_2	$BeSO_4$	Mix. of Soluble Salts	Lost Time Days	BeF_2	$BeSO_4$	Mix. of Soluble Salts	Lost Time Days	BeF_2	$BeSO_4$	BeF_2	$BeSO_4$	
1940	....	....	....	....	....	1	....	....	....	....	....	....	....
1941	....	1	1	86	....	1	....	....	....	3	....	....	....
1942	3	3	....	219	3	7	3	81	4	4	1	1	18
*1943	1	....	5	162	5	10	9	397	5	5	....	....	71
1944	....	....	5	477	....	5	2	214	5	5	....	1	92
1945	7	....	....	228	9	6	4	578	12	9	4	....	240
1946	2	....	1	232	9	....	2	208	13	....	5	....	132
1947	14	2	5	644	25	5	7	627	51	9	33	6	740
1948	6	1	....	261	5	2	1	95	7	2	5	....	80
1949	....	....	....	....	....	....	....	....	3	....	5	....	64
1950	2	1	....	93	5	1	1	164	7	....	2	....	86
**1951	....	....	....	....	1	....	....	40	2	....	....	....	15
Total	35	8	17	2402	62	38	29	2404	109	37	55	8	1538

*1943—Three fatalities.
**Complete to July, 1952.

Table 2

SUMMARY OF SURVEY OF 10 WORKERS WITHOUT HISTORY OF BERYLLIUM INTOXICATION*

1952

Case No. Sex Present Age	Length of Service in Be Industry	Exposure	24 Hour Urine Analysis		Present Status
			Date of Analysis and Laboratory	Micrograms Be/L	1) Physical 2) Vital capacity 3) Chest x-rays
1 Female 49 years	4-22-43 to 7-31-48 5 years	Beryllium oxide	3-5-52 (K)	0.10	Normal
2 Female 52 years	4-23-43 to 9-1-48 5 years	Beryllium oxide	3-5-52 (K)	0.38	Normal except for fibrosis of lower lungs present previous to employment.
3 Female 31 years	5-17-43 to January 1950 6½ years	Beryllium oxide	Not obtained		Normal
4 Male 50 years	1926 to present 26 years	All phases of production/maintenance since 1940	1-2-52 (A)*	0.20	Normal
5 Male 58 years	3-14-37 to present 15 years	Mainly beryllium oxide. In office since 1950.	1-2-52 (A)*	1.80	Normal
6 Male 40 years	1937 to present 15 years	All phases of BeO production. Fluoric processes since 1940.	1-2-52 (A)*	3.0	Normal
7 Male 34 years	2-2-40 to present 12 years	Plant production	1-2-52 (A)*	1.80	Normal
8 Male 39 years	5-4-42 to present 10 years	Maintenance	1-2-52 (A)*	0.20	Normal
9 Male 38 years	7-1-47 to present 5 years	Chemist in analytical laboratory.	1-2-52 (A)*	0.50	Normal
10 Male 24 years	10-4-49 to present 3 years	In all phases of beryllium extraction	1-2-52 (A)*	0.20	Normal

*Fluorimetric determination by Laboratory (A).

Male 24 years	3 years	In all phases of beryllium extraction	1-2-52 (A)*	0.20	Normal

*Fluorimetric determinations by Laboratory (A).

Table 3

SUMMARY OF NECROPSY ANALYSES OF TISSUES AND URINE IN 2 CASES OF MAJOR RESPIRATORY BERYLLIUM POISONING (RECOVERIES)

Case No. Date of Analysis & Laboratory	Lung micrograms Be/100 Gm.	Liver micrograms Be/100 Gm.	Heart micrograms Be/100 Gm.	Spleen micrograms Be/100 Gm.	Kidney micrograms Be/100 Gm.	Urine micrograms Be/L
1 1-26-51(K)	182.			0.94	2.15	
2 8-9-51 (K) 8-15-51 (A) 8-1-50 (A)	153.0 2.0	12.5 0.72	0.36 0.17	3.15 0.95		 0.60

Table 4

FOLLOW-UP SURVEY OF 20 CASES OF ACUTE (BERYLLIUM) TRACHEOBRONCHITIS OVER PERIOD 11 YEARS

Case No. Sex Present Age	Length of Service in Be industry	Dates of Occupational Disease	24 Hour Urine Analysis		Present Status
			Date of Analysis and Laboratory	Micrograms Be/L	1) Physical 2) Vital capacity 3) Chest x-ray
1 Male 52 years	Since 1926 26 years	9-20-43 to 9-30-43	4-1-48 (K) 11-15-51 (K) 1-2-52 (A)*	0.80 1.84 0.90	Normal. Still working in beryllium production.
2 Male 48 years	Since 1936 16 years	1-25-44 to 2-9-44 2-21-44 to 3-1-44	4-1-48 (K) 10-30-51 (K) 1-2-52 (A)*	0.60 2.50 0.60	Normal. Still working in beryllium production.
3 Male 39 years	Since 1937 15 years	6-30-43 to 7-7-43 9-9-46 to 9-16-46	7-12-50 (A)*	0.60	Normal. Still working in beryllium production.
4 Male 36 years	Since 1940 12 years	7-10-46 to 7-16-46 4-9-47 to 4-20-47	10-30-51 (K) 1-2-52 (A)*	3.55 2.90	Normal. Still working in beryllium production.
5 Male 32 years	Since 1941 11 years	12-17-46 to 12-26-46	11-15-51 (K) 1-2-52 (A)*	10.60 4.40	Normal. Still working in beryllium production.
6 Male 33 years	Since 1941 11 years	3-20-47 to 3-31-47	11-15-51 (K) 1-2-52 (A)*	0.72 0.20	Normal. Still working in beryllium production.
7 Male 41 years	Since 1945 7 years	6-13-45 to 7-9-45	11-15-51 (K) 1-2-52 (A)*	4.20 1.70	Normal. Still working in beryllium production.
8 Male 45 years	Since 1947 5 years	5-26-47 to 6-9-47	10-30-51 (K) 1-2-52 (A)*	0.18 0.20	Normal. Still working in beryllium production.
9 Male 50 years	From 1940-1944 4 years	4-3-44 to 4-29-44	7-12-51 (A)* 10-16-51 (A)*	0.70 0.20	Normal
10 Male 39 years	In 1942-1943 9 months	6-16-43 to 6-30-43	11-15-51 (K) 10-14-51 (A)*	0.50 3.20	Normal

SURVEY OF 20 CASES OF ACUTE (BERYLLIUM) TRACHEOBRONCHITIS OVER PERIOD
11 YEARS

Male 39 years	9 months	8-18-43 to 8-30-43	11-15-51 (K) 10-14-51 (A)*	0.50 3.20	Normal

SURVEY OF 20 CASES OF ACUTE (BERYLLIUM) TRACHEOBRONCHITIS OVER PERIOD
11 YEARS

Case No. Sex Present Age	Length of Service in Be Industry	Dates of Occupational Disease	24 Hour Urine Analysis		Present Status
			Date of Analysis and Laboratory	Micrograms Be/L	1) Physical 2) Vital capacity 3) Chest x-ray
11 Male 33 years	In 1943 43 days	3-13-43 to 3-24-43	7-12-51 (A)*	0.40	Normal
12 Male 49 years	In 1943 4 years	11-8-43 to 11-22-43	11-15-51 (K) 10-11-51 (A)*	0.43 0.20	Normal
13 Female 40 years	In 1943 5 months	9-29-43 to 10-6-43	7-13-51 (A)* 1-2-52 (A)*	0.65 0.20	Normal
14 Male 48 years	In 1944 2 months	1-15-44 to 3-20-44	6-17-48 (K) 7-21-50 (A)* 11-15-51 (K) 1-2-52 (A)*	0.04 nil 0.35 0.01 nil 0.20	Normal
15 Male 43 years	In 1944 1½ months	1-29-44 to 4-5-44	6-21-48 (K) 7-12-51 (A)*	0.04 nil 0.25	Normal
16 Male 38 years	In 1945 6 months	6-20-45 to 7-17-45	7-25-50 (A)* 11-15-51 (K) 10-14-51 (A)*	0.60 0.14 0.20	Normal
17 Male 60 years	In 1945 4 months	11-7-45 to 12-17-45	11-15-51 (K) 10-5-51 (A)*	0.05 0.20	Normal
18 Male 28 years	In 1946 2 months	3-20-46 to 4-15-46	11-15-51 (K) 1-2-52 (A)*	1.32 3.00	Normal
19 Male 51 years	In 1947 16 days	2-20-47 to 3-20-47 and 3-25-47 to 4-14-47	7-12-51 (A)*	0.20	Normal
20 Male 25 years	In 1947-1948 11 months	7-20-47 to 7-28-47	11-15-51 (K) 1-2-52 (A)*	0.08 0.20	Normal

*Fluorimetric method of analysis.

Table 5

FOLLOW-UP SURVEY OF 20 CASES OF ACUTE (BERYLLIUM) PNEUMONITIS OVER PERIOD 11 YEARS

Case No. Sex Present Age	Length of Service in Be industry	Dates of Occupational Disease	24 Hour Urine Analysis		Present Status
			Date of Analysis and Laboratory	Micrograms Be/L	1) Physical 2) Vital capacity 3) Chest x-ray
1 Male 46 years	Since 1940 12 years	1-13-48 to 2-2-48	11-15-51 (K) 1-2-52 (A)*	7.40 4.50	Normal. Still working in industry.
2 Male 59 years	Since 1941 11 years	4-4-41 to 4-29-41	4-1-48 (K) 1-2-52 (A)*	1.20 1.10	Normal. Still working in industry.
3 Male 30 years	Since 1946 5½ years	10-20-46 to 11-27-46	4-1-48 (K) 10-30-51 (K) 1-2-52 (A)*	0.40 0.26 0.40	Normal. Still working in industry.
4 Male 37 years	Since 1947 4 years	2-24-47 to 4-29-47	4-1-48 (K) 9-8-48 (K)	0.30 0.30	Normal. Still working in industry.
5 Male 30 years	Since 1947 5 years	12-25-47 to 1-19-48	11-15-51 (K) 1-2-52 (A)*	0.70 0.20	Normal. Still working in industry.
6 Female 27 years	1943 to 1947 4 years	4-5-47 to 5-12-47	11-15-51 (K) 10-26-51 (A)*	0.28 0.20	Normal
7 Female 49 years	In 1943 2 months	8-7-43 to 12-6-43	8-2-48 (K) 10-8-51 (A)*	Nil 0.20	Normal
8 Male 54 years	In 1944 3 months	5-25-44 to 9-21-44	6-29-49 (K) 1-2-52 (A)*	0.04 nil 0.20	Pulmonary fibrosis with decreased V.C. to 60% of normal.
9 Male 57 years	In 1944 6 months	1-16-45 to 4-2-45	No specimen	....	Normal
10 Male 57 years	In 1945 3 months	6-6-45 to 7-5-45	7-12-51 (A)*	0.20	Normal

FOLLOW-UP SURVEY OF 20 CASES OF ACUTE (BERYLLIUM) PNEUMONITIS OVER PERIOD 11 YEARS

10 Male 57 years	In 1945 3 months	6-6-45 to 7-5-45	7-12-51 (A)*	0.20	Normal

FOLLOW-UP SURVEY OF 20 CASES OF ACUTE (BERYLLIUM) PNEUMONITIS OVER PERIOD 11 YEARS

Case No. Sex Present Age	Length of Service in Be industry	Dates of Occupational Disease	24 Hour Urine Analysis		Present Status
			Date of Analysis and Laboratory	Micrograms Be/L	1) Physical 2) Vital Capacity 3) Chest x-ray
11 Male 28 years	In 1945 3 months	7-13-45 to 9-4-45	11-15-51 (K) 1-2-52 (A)*	0.20 0.22	Normal
12 Male 27 years	In 1946-1947 3 months	11-25-46 to 3-31-47	9-23-49 (K)	0.04	Normal
13 Male 68 years	In 1946-1947 4 months	1-11-47 to 1-28-47 4-1-47 to 4-12-47	7-14-48 (K)	0.04	Normal
14 Male 46 years	In 1947 2 months	3-8-47 to 3-24-47	7-18-50 (A)* 11-15-51 (K) 1-2-52 (A)*	0.40 0.03 0.20	Normal
15 Female 38 years	In 1947 5 months	5-14-47 to 6-30-47	7-12-51 (A)* 11-28-51 (K) 11-12-51 (A)*	0.55 0.034 0.20	Normal
16 Male 29 years	In 1947 3 months	7-3-47 to 8-27-47	11-15-51 (K) 10-26-51 (A)*	0.01 0.20	Normal
17 Male 45 years	In 1947 3 months	9-13-47 to 10-8-47	7-21-51 (A)*	0.60	Normal
18 Male 39 years	In 1947 2 months	11-5-47 to 12-22-47	7-12-51 (K) 1-2-52 (A)*	0.065 0.40	Normal
19 Male 30 years	In 1947 23 days	10-29-47 to 12-9-47	8-13-48 (K) 11-1-51 (A)*	0.04 1.40	Normal
20 Female 46 years	In 1947-1948 2 months	1-6-48 to 1-13-48	10-16-51 (A)*	2.30	Normal

*Fluorimetric method of analysis.

Table 6

SUMMARY OF TISSUE ANALYSES OF 5 AUTOPSIED CASES CHRONIC BERYLLIOSIS

Case No. Sex Age at Death	Type of Exposure and Duration	Dates of Onset of disease to Death	Date of Analysis and Laboratory	Lung Microgram Be/100 Gm.	Liver Microgram Be/100 Gm.	Broncho-pulmonary Lymph nodes Microgram Be/100 Gm.	Spleen & Bone Micrograms Be/100 Gm.	Other Tissue Micrograms Be/100 Gm.	Urine Microgram Be/Liter
1 Female 38 yrs.	Neighborhood: Lived 2 blocks from plant 1940 to 1945	Jan. 1944 to 7-15-46	12-19-47(K) 8-11-48 (S)	Nil 0.4					
2 Female 26 yrs.	Neighborhood: lived ½ mile from plant in 1941.	June 1946 to Feb. 17, 1948	3-23-48 (K) 6-3-48 (R)	.93 .08	1.48 .05	6.5	Spleen 0.17	Kidney .07	
3 Female 7 yrs.	Neighborhood: Lived ½ mile from plant 1941 to 1947.	March 1947 to 9-4-48	9-25-48 (K)	0.237	Nil or 0.008	0.665	Spleen nil or 0.02		
4 Female 53 yrs.	Neighborhood: Lived ½ mile from plant 1942 to 1949.	May 1947 to 8-24-49	12-20-48(K) 3-6-50 (A) Sept.1949(K) Sept.1949(R)	.... 0.2 Nil Nil	....	.... 10.0 0.59 Nil	.... Rib 7.7 Rib nil Rib nil	.... Heart 10.0	Nil or .002
5 Female 26 yrs.	Household: Husband's clothing. Dec. 1942 & Jan. 1943.	Dec. 1943 to 11-27-49	4-1-49 (K) 12-20-49(K) 3-6-50 (A) 3-9-50 (R)	.... 0.99 .... 0.11	.... 0.68 0.40 Nil	.... 5.0 3.3	.... Spleen 0.7 Spleen 0.03	....	Nil

SUMMARY OF SURVEY OF 12 LIVING PATIENTS WITH CHRONIC BERYLLIOSIS**

SUMMARY OF SURVEY OF 12 LIVING PATIENTS WITH CHRONIC BERYLLIOSIS**

Sex Present Age	Type of Exposure	Dates of Exposure	Date of Onset of Disease	24 Hour Urine Sample		Blood Analyses		Present Status and Therapy
				Date of Analysis and Laboratory	Micrograms Be/L	Date of Analysis and Laboratory	Micrograms Be/100 Gm.	
1 Female 40 yrs.	Nonoccupational. Laundered brother's clothing.	Brother worked at plant in 1941 and 1942	In 1944	8-7-50 (A)* 11-15-51 (K) 1-2-52 (A)*	0.70 0.22 0.20	8-10-50 (K)	Nil	Slight improvement. Symptomatic, conservative therapy.
2 Female 27 yrs.	Nonoccupational.	Lived 1 block from plant 1940 to 1948	February 1947	4-1-48 (K) 8-8-50 (A)*	Nil 0.35	8-10-50 (K)	Nil	Improving. Symptomatic, conservative.
3 Male	Nonoccupational. (Same dwelling as Case 2)	Lived 1 block from plant Feb. 1948 to 1952.	May 1948	10-1-50 (A)*	0.55	8-10-50 (K)	Nil	Condition worse. Therapy unknown.
4	Nonoccupational	Lived 100 feet from plant from Nov. 1940 to April 1945	April 1942	1-2-52 (A)*	3.70	10-23-50 (K)	0.01	Improving. Symptomatic, conservative therapy.
5 Female 33 yrs.	Nonoccupational	Lived 1 block from plant 1942 to 1947.	Fall 1946	4-1-48 (K) 8-8-50 (A)* 11-15-51 (K) 1-2-52 (A)*	0.13 0.35 0.06 0.20	8-11-50 (K)	Nil	Improving. Symptomatic, conservative therapy.
6 Male 24 yrs.	Nonoccupational	Exposed to father's clothing; a plant employee from 1940 to 1952.	March 1949			8-10-50 (K)	Nil	Improving; special therapy.

**Survey, data to July 1952.

(continued on page 192)

*Fluorimetric method used by Laboratory (A) in 1951 and 1952.

Table 7—(Continued from page 191)

SUMMARY OF SURVEY OF 12 LIVING PATIENTS WITH CHRONIC BERYLLIOSIS**

Sex Present Age	Type of Exposure	Dates of Exposure	Date of Onset of Disease	24 Hour Urine Sample		Blood Analyses		Present Status and Therapy
				Date of Analysis and Laboratory	Micrograms Be/L	Date of Analysis and Laboratory	Micrograms Be/100 Gm.	
7 Female 61 yrs.	Nonoccupational	Lived ½ mile south of plant since 1923 to present.	April 1950	6-30-52 (K)	0.16			Improved in last 12 months. No therapy.
8	Occupational	June 1, 1941 to July 3, 1941	Dec. 1944	4-1-48 (K) 11-15-51 (K) 1-2-52 (A)*	0.14 0.58 1.50			Slight improvement. Symptomatic, conservative therapy.
9 Male 31 yrs.	Occupational	Dec. 1941 and Jan. 1942	Jan. 1946	Not obtained		Not obtained		Some improvement. Symptomatic, conservative therapy.
10 Male 35 yrs.	Occupational	June 14, 1944 to July 13, 1944	Late 1947	11-15-51 (K) 7-12-51 (A)* 1-2-52 (A)*	0.09 0.75 1.40	11-9-50 (K)	Nil	Improving but totally disabled. Cortisone.
11 Female 43 yrs.	Occupational	Nov. 1943 to Mar. 1944	Dec. 1947	12-26-50 (A)* 11-15-51 (K) 1-2-52 (A)*	0.65 0.06 0.42	1-4-51 (K)	Nil	Improving. Partial disability. Symptomatic, conservative therapy.
12 Male 53 yrs.	Occupational	4-30-45 to 5-30-45 7-9-45 to 7-19-45	Oct. 1947	6-21-48 (K) 7-12-51 (A)* 11-15-51 (K) 1-2-52 (A)*	0.04 1.00 0.01 0.20	1-10-51 (K)	Nil	Some improvement. Total disability. Cortisone therapy.

**Survey, data to July 1952.
*Fluorimetric method used by Laboratory (A) in 1951 and 1952.

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CARDIAC ARREST

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UNEXPECTED cessation of the heart beat is the most serious of all operating room complications. If the patient does not have underlying cardiac disease this complication must be attributed directly to the anesthesia or to the surgical procedure. Popular acceptance of an entity is always followed by apparent increase in incidence; nevertheless we believe that cardiac arrest is occurring with greater frequency. We attribute this to more complicated anesthetic technic coupled with the surgeon's demand for longer and deeper level anesthesia. As more cases of cardiac arrest are reported, the emphasis appears to be on recognition and immediate therapy by surgical intervention. Equally important, in our opinion, is the greater need for emphasizing the cause of this unfortunate complication and its prevention.

Experience

During the last 4 years there have been 19 cases of proved cardiac arrest in the Cleveland Clinic. Prior to this time there were operating room deaths attributed to various causes such as apoplexy, coronary occlusion, embolus, drug reaction, status thymicolymphaticus, and shock; cardiac arrest, as a clinical entity, was not known. Regardless of the true cause of death in the early series, the present group of 19 proved cases represents a distinct increase in incidence. By "proved cases" we mean visual evidence of cardiac arrest during thoracotomy for resuscitation. Severe cyanosis, accompanied by imperceptible pulse, heart beat and blood pressure, is not conclusive evidence of arrest; as mentioned by Lahey and Ruzicka, spontaneous recovery may occur in this formidable state.[1] Spontaneous recovery does not occur in cardiac arrest.

These 19 cases have been distributed over most of the surgical and allied specialty services. In each instance a distinct effort has been made to critically evaluate the factors producing the arrest by presenting the case at open meeting for frank evaluation. Emphasis has been placed on the preoperative medication, anesthesia agents, position on the table, level of anesthesia, and nature of the procedure; every effort has been made to evaluate the patient's condition prior to surgery, and the anesthesia course immediately preceding the accident. Whereas one cannot expect the results of such an investigation to be accurate or even worth while in every instance, we believe that a better clinical understanding of the problem has resulted from these studies. In essence, the clinical observations gained from these 19 cases tend to confirm the experimental observations of Wiggers, Beck, Sloan, Young, and others who have

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investigated the cause and treatment of cardiac arrest.[2,3,4,5,6,7,8] Emergency thoracotomy for diagnosis and therapy was employed in every case. It is significant that ventricular fibrillation did not occur in this group of patients. After massage of the heart and control of respiration a sinus rhythm was established in each instance. This limited series tends to support Harris' contention that the reported rate of ventricular fibrillation is too high;[9] Harris states that the feeble undulations detected by electrocardiography in the failing heart do not contribute to death but are frequently interpreted as true fibrillation.

In the laboratory, arrest of a dog's heart may be produced by electric shock,[4] overdosage of drugs,[10] prolonged asphyxia or vagal stimulation in the presence of hypoxia.[7,8] It is the latter method that appears to be of greatest clinical significance. We believe that two factors are productive of cardiac arrest in the human heart; hypoxia and vagal inhibition. The search for a common denominator in 19 cases in which various anesthetic technics and surgical procedures were employed has led us to believe that oxygen deficiency coupled with vagal depression must be present to arrest a normal heart. These observations tend to corroborate the excellent work of Beck and Wiggers, who have repeatedly created the accident within the laboratory and have emphasized its clinical importance.[2,3,4,5,6] Most recently Sloan has shown the more exact relationship between hypoxia and vagal inhibition in producing arrest of the dog's heart.[7]

Another factor we believe to be of importance is hypercapnia associated with carbon dioxide retention. Two of our patients (table 1) both children approximately 2 years of age, suffered cardiac arrest after mechanical impairment of the endotracheal airway. Beecher[11] has emphasized the significance of high carbon dioxide tension during anesthesia and has repeatedly warned of its danger. According to Beecher the excessive retention of carbon dioxide within alveoli produces hypercapnia and acidosis; tachycardia and hypertension are clinical manifestations of increasing carbon dioxide retention. In the two cases mentioned there was mechanical impairment of the airway; the endotracheal tube had passed the carina creating occlusion of one bronchus and effectively reducing the ventilation of the contralateral lung. Both children developed progressive tachycardia and hypertension with abrupt onset of bradycardia and eventual arrest.

Hypoxia or stimulation of the vagi alone may produce serious alteration of the conductive mechanism in the heart with resultant hypotension and bradycardia. Regardless of the cause, the alteration in normal physiology is both recognizable and reversible. When both factors are present, however, depression of the heart may result in complete absence of conduction and arrest occurs.[7,8,9] In this event, release of the factor that is producing either hypoxia or vagal inhibition will not be effective unless active measures are taken to restore the heart beat mechanically. The clinical errors that produce both oxygen deficit and vagal stimulation are shared by the anesthetist and the surgeon. We believe that the commonest factors attributable to each may be categorized under two headings:

1. Anesthesia factors:
   a) Multiplicity of agents.
   b) Overdosage.
   c) Obstruction of airway.
   d) Injudicious use of tracheal aspiration.
   e) Complexity of technic.
2. Surgical factors:
   a) Insistence on "deep" anesthesia.
   b) Excessive tissue trauma.
   c) Inadequate blood or fluid replacement.
   d) Hyperpyrexia.
   e) Unphysiologic position of the patient—or abrupt changes of patient's position.

It must be emphasized that these clinical items are based on observation in the operating room and critical analyses of case histories of proved arrest. To what degree any one factor may produce oxygen deficit or create vagal stimulation is difficult to state. Nevertheless each of the listed factors has merited comment and elicited warnings by writers in the past. Potts has emphasized the importance of using minimum doses of medicine and as few agents as possible, since all are poisons;[12] he prescribes no barbiturates for children. Instances of hypoxia resulting from respiratory depression with excessive doses of morphine, pentothal or nitrous oxide, are familiar to all. Hyperpyrexia secondary to fever, dehydration, excessive draping of the patient or use of overheated operating rooms, will increase the oxygen requirement; in children[12] or severely ill adults, a serious oxygen deficiency may be created by uncontrolled body heat. Likewise the depletion of the patient's tidal volume by careless aspiration of the trachea and major bronchi under deep anesthesia is productive of temporary anoxia. The bronchial spasm produced by intubation under improper anesthetic level may be accompanied by impressive cyanosis, indicating profound hypoxia. Whereas changes in normal physiology occur frequently without serious consequences in operating rooms everywhere, the combination of unnecessary oxygen deficit with vagal inhibition under satisfactory conditions may result in fatal accidents.

Once cardiac arrest has occurred, the initiating factors may be obscured by the excitement and confusion that inevitably follows. The impression produced by a single case may have a profound effect upon both surgeon and anesthetist; more important, the impressions may be based on error and exert no value in prevention of future accidents. Too often the human tendency is to place the responsibility upon the patient and his disease. However, a critical analysis of every record obtainable assures a progressively clearer and more accurate understanding of the problem.

Whereas the sequence of events preceding cardiac arrest may be variable or obscure, a pattern of alteration in hemodynamics does occur. In most instances premonitory signs may be present and should be recognized if the accident is to be averted. Cyanosis always implies oxygen need and is a warning

sign! Hypoxia will usually produce a transient tachycardia, and perceptible elevation of blood pressures before the more serious duo of bradycardia and hypotension appear. Abrupt slowing of the pulse rate with accompanying hypotension is the predominant sign and invariably precedes arrest. An alert team of surgeon and anesthetist will accept this warning of impending disaster and make every effort to recognize and correct the underlying factor. To do so may abort the cardiac arrest as the circulatory alteration is still reversible.

Prevention

Of primary importance in prevention of cardiac arrest is recognition of the factors that may initiate oxygen deficit and vagal stimulation as well as the signs of impending cessation of heart beat. When the patient's condition shows definite change under anesthesia manifested by cyanosis, bradycardia and falling blood pressure, the alarm must be sounded. This alteration in hemodynamics may occur in the induction phase of anesthesia just as easily as in the course of a long complicated operation. At no time during the interval between the patient's induction and his return to consciousness are the patient and anesthetist entirely free of this potential hazard.

When the signs of impending arrest are recognized, the responsibility for correction of the cause of the factor falls equally on the surgeon and the anesthetist. Each must play his part in averting catastrophe.

1. Surgeon's Role:
   a) Abandon the operative procedure.
   b) Prepare to open the chest if arrest ensues.
   c) Assist in correcting blood deficit if this is a factor.
2. Anesthetist's Role:
   a) Establish airway; prompt intubation if needed.
   b) Control respiration with 100 per cent oxygen.
   c) Intravenous atropine sulfate.
   d) Continuous evaluation of pulse and blood pressure.

By sharp division of responsibility, unnecessary reduplication and confusion are avoided. When such emergency arises, those present must manage the problem; this is no time for frantic consultation with cardiologists or trusted colleagues who may be elsewhere in the hospital. Likewise, efforts by the surgeon to employ the time-honored methods of artificial respiration are only added hazards to the patient. Actually a calm, prompt effort to correct the anoxia by positive pressure via a patent airway, combined with release of the vagal stimulation by intravenous atropine sulfate, will usually suffice to abort the impending arrest.

Atropine sulfate may be an invaluable drug in such emergencies. This drug inhibits the parasympathetic effect of the vagus and its depressant action on the heart. The dosage will vary with the age and the size of the patient. The infant will tolerate a dose of 1/1000 gr. (Potts), the adult should receive 1/100 gr., or more. In all instances the drug must be given intravenously, as the

Department	Age	Physical Cond.	Scheduled Procedure	Anesthesia	Time of Arrest	Management	Outcome	Remarks
1. General Surg.	58	Fair	Whipple op. ca. pancreas	Continuous spinal and pentothal	Midway in operation	Delayed subdiaphragmatic massage and intracardiac adrenalin	Death on table	Anoxia due to hypotensive state; low blood volume secondary to inadequate replacement.
2. General Surg.	36	Good	D & C	Spinal and pentothal	Induction	Transthoracic massage	Recovery, complete	Preop. hemoglobin 8.0 Gm.; arrest followed lowering legs from lithotomy position.
3. General Surg.	46	Good	Vagotomy	Spinal and pentothal	Termination of operation	Transthoracic massage	Recovery, permanent cortical damage	Pentothal given to supplement waning spinal; respirations not assisted.
4. General Surg.	8	Fair	Excision of neuroblastoma left adrenal	Pento. induct. endotracheal GOE	Midway in operation	Transthoracic massage	Recovery—death in 6 hours due to cerebral decortication	Hypotensive state secondary to severe blood loss.
5. Neurosurgery	29	Good	Cervical rhizotomy	Pento. with endotracheal N_2O-O_2	During skin incision	Transthoracic massage	Recovery, complete	Induced hypotension (Page procedure) in upright position under anesthesia.
6. Neurosurgery	29	Good	Laminectomy	Spinal and pentothal	Induction	Transthoracic massage	Recovery—death in 1 week due to cerebral decortication	Abrupt change in position, supine to prone, under anesthesia—inadequate airway.
7. General Surg.	37	Good	Vagotomy	Spinal and pentothal	Prior to closure	Transthoracic massage	Recovery, complete	Mechanical obstruction of airway followed by cyanosis, bradycardia and arrest.
8. Thoracic Surg.	69	Fair	Esophageal resection	Pento. induction endo. GOE	Induction	Transthoracic massage	Recovery, complete	ECG evidence of acute coronary occlusion.
9. Thoracic Surg.	27 mos.	Fair	Patent duct	Endo. GOE	Completion of operation	Transthoracic massage	Recovery—died 48 hrs. later, cerebral damage	Hypercapnia due to CO_2 retention—endobronchial tube below carina.
0. Thoracic Surg.	62	Poor (gr. III heart d.)	Exploratory thoracotomy	Pento. induction endo GOE	Induction	Transthoracic massage	Recovery—died 7 days after, no cerebral damage	ECG evidence and postmortem evidence of myocardial infarction during induction.
11. Thoracic Surg.	16 mos.	Fair	Division patent duct	Endo GOE	Induction	Transthoracic massage	Recovery, complete	Hyperthermia, followed by hypercapnia with CO_2 retention. Operation completed after [illegible]
12. Thoracic Surg.	66	Poor	Repair dia-	Pento. in-	Completion	Transthoracic	Recovery—	Postmortem evidence of cor-

Department	Age	Status	Procedure	Anesthesia	Arrest	Management	Outcome	Remarks
11. Thoracic Surg.	16 mos.	Fair	Division patent duct	Endo GOE	Induction	Transthoracic massage	Recovery, complete	Hyperthermia, followed by hypercapnia with CO_2 retention. Operation completed after resuscitation.
12. Thoracic Surg.	66	Poor (grade IV heart d.)	Repair diaphragmatic hernia	Pento. induction	Completion of operation	Transthoracic massage	Recovery—died 10 days	Postmortem evidence of coronary infarction.
13. Thoracic Surg.	55	Poor (grade III heart d.)	Pericardectomy	Pento. and cocaine 4% induction	Following intubation	Transthoracic massage	Recovery, complete	Severe heart disease—arrest followed minimal anoxia associated with intubation.
14. Urologic Surg.	8 mos.	Fair	Nephrostomy (Urinary fistula following ureterosigmoidostomy	Ether	Induction	Transthoracic massage	Recovery, complete	Hypoxia secondary to massive l. hydrothorax. Marked impairment in pulmonary function at time of induction.
15. General Surg.	67	Fair	Ant. resection sigmoid	Continuous spinal; pentothal supplement	Midway in operation	Transthoracic massage	Recovery, complete	Obese patient in deep Trendelenburg's position—anoxia due to thoracic compression plus respiratory depression by pentothal without mechanical airway.
16. Ophthalmologic Surg.	65	Good	Enucleation cataract	Pentothal	Midway in operation	Transthoracic massage	Recovery—death in 3 hours from cerebral decortication	Anoxia due to inadequate airway—cyanosis not recognized under drapes.
17. Otolaryngologic Surg.	57	Poor	Bronchoscopy	Topical cocaine 4%	40 minutes after anesthesia (bronchoscopy cancelled)	Transthoracic massage	Recovery—death in 1 hour due to cerebral decortication	Chronic hypoxia with severe cardiopulmonary disease; anoxia precipitated by severe bronchospasm with topical anesthesia.
18. Thoracic Surg.	52	Poor	Bronchoscopy	Topical cocaine 4%	15 minutes after endoscopic procedure	Transthoracic massage	Recovery—minimal added cortical damage	Note: Diag. cardiac arrest made 3 months before during treatment elsewhere for intractable asthma; recovered with marked personality change.
19. Neurosurgery	37	Poor	Suboccipital craniotomy	Pentothal and local (procaine 1%)	During removal of skull plate	Transthoracic massage	Unable to restore normal heart rate	Pressure on medulla by intracranial cyst producing paralysis of respiratory center.

Table. An effort has been made to give a digest of the pertinent information concerning each of the 19 cases of proved cardiac arrest. Under the subject OUTCOME the term RECOVERED is used whenever the quiescent heart has been resuscitated and sinus rhythm restored. This does not mean that the patient has been saved; the ultimate fate of the patient is recorded separately.

failing circulation may not assimilate a subcutaneous or intramuscular medication.

Restoration of normal pulse and blood pressure is synonymous with correction of the underlying causative factor. There should be no residual cortical damage associated with this phase of hypoxia. The election as to continuation or abandonment of the surgical procedure is a matter of judgment. This decision will depend entirely upon the circumstances associated with the individual case.

Therapy

Much has already been written upon the surgical treatment of cardiac arrest. Nevertheless, for the sake of completeness and for the importance that the problem merits, a certain amount of repetition is justifiable.

Again we believe that the responsibility of therapy must be divided between the surgeon and the anesthetist. Each must carry out his assignment with dispatch and with a minimum of confusion and duplication of effort.

1. Surgeon's Responsibility:
   a) Prompt thoracotomy—4th, 5th, or 6th anterior interspace, left.
   b) Manual compression of the arrested heart for restoration of circulation.
   c) Visual inspection of the heart if recovery is not reasonably prompt.
   d) Intracardiac epinephrine, only (1) if restored beat is feeble, or (2) if there is no spontaneous recovery of beat following continuous manual compression.

Any incision that will give adequate access to the arrested heart is satisfactory. We do believe that the most desirable approach is through the left anterior thorax; the incision should be made with whatever blade is available and with complete disregard for the usual operating room rituals of skin sterilization and wound draping. Upon opening the chest it may be necessary to cut or fracture a costal cartilage to permit entry of the surgeon's hand. The wound may be retracted by the assistant employing his fingers or any form of available retractor. It is not necessary to open the pericardium, and manual compressions should be started immediately. The rate of compression will depend entirely on the rate of filling of the inert heart. Frequently the cardiac rhythm will respond promptly with only a few compressions by the surgeon's hand. When this occurs no further therapy need be carried out, but a period of observation is in order before closing the thoracic wound. When the heart beat is feeble or fails to return spontaneously, then intracardiac epinephrine in small doses is indicated. It has been our custom to use approximately ¼ cc. of epinephrine 1:1000 directly into the left ventricular chamber. Closure of the chest wall is a minor problem and can be accomplished with pericostal chromic catgut sutures and whatever material is available for closure of the muscle and skin layers.

2. Anesthetist's Responsibility:
   a) Prompt intratracheal intubation.
   b) Oxygen 100 per cent under intermittent positive pressure.
   c) Intravenous atropine sulfate, if bradycardia follows restoration of heart beat.

The importance of positive pressure oxygen therapy in resuscitation of the heart cannot be overemphasized. This is best carried out by means of a closed system employing the endotracheal tube. When properly executed, intermittent positive pressure anesthesia in itself can maintain a demonstrable circulation of blood through the lungs and to the brain. Correction of the anoxia by the anesthetist and intravenous administration of atropine sulfate, if indicated, will correct the initiating factors of hypoxia and vagal inhibition that produced the cardiac arrest.

Restoration of a normal sinus rhythm is not necessarily indicative of a return to normal physiology. Severe cortical damage will follow brief periods of anoxia and central nervous system damage may follow. It is for this reason that the emphasis on speed of recognition and initiation of therapy cannot be overemphasized. The exact period of time that may elapse between the onset of anoxia and severe cerebral damage is not known. It is dangerous for the surgeon to rely upon an arbitrary time interval before initiating the course of therapy that is clearly indicated.

Discussion

Cardiac arrest is a complication of anesthesia and surgery and is rarely a primary disease. For this reason we must look to ourselves in seeking the cause of a given accident; to blame the patient and his disease is fundamentally misleading. This unfortunate error has occurred more frequently than we care to admit even though it is often classified by another term. Every experienced surgeon and anesthetist can recall instances of sudden death that may well have been due to cardiac arrest.

In our experience cardiac arrest has occurred more often in the good risk patient than in the so-called bad risk person who is being subjected to a surgical procedure. This is an important observation on the principal causes of cardiac cessation which have been discussed. When a poor risk patient is brought to surgery meticulous care is used in the selection of anesthesia agents and he is closely scrutinized during the induction and subsequent course of anesthetic administration. Usually such a patient is subjected to the least amount of trauma and blood loss and is invariably given the benefit of a high supplementary oxygen intake. It is undoubtedly the combination of careful observation and basic precautions which eliminate the causative factors of cardiac arrest in these cases. The higher mortality rate associated with the poor risk patient is explained on complications other than true cardiac arrest. It is for this reason that the tragic sequela to cardiac arrest in the so-called

FIG. 1. Usual site of emergency thoracotomy for cardiac resuscitation is illustrated by diagram. Manual compression of the heart to maintain blood flow may be performed by alternate use of right and left hands to combat fatigue. The element of time is too precious to be sacrificed for technic! When necessary, resuscitation must be performed through an unprepared field by bare hand.

good risk patient must be kept in mind by all who practice surgery and anesthesiology. Until we are willing to accept the precursors of cardiac arrest as avoidable errors attributable directly to the anesthetist and surgeon there is little possibility that this dreaded accident will be eliminated from the list of operating room complications.

In the manner of the old fashioned fire drill it might be well for all surgeons and anesthetists to anticipate this tragedy and analyze the causative factors in past cases. Elimination of potential cause for hypoxia will, in itself, almost completely exclude the possibility of cardiac arrest in the good risk patient. A clear understanding of the roles of the anesthetist and surgeon in cardiac resuscitation may be of tremendous value in avoiding procrastination and confusion. Most important is a frank acceptance on the part of the operating team of the exact nature of the complication and its cause. The only stigma attributable to a case of cardiac arrest is that associated with failure to recognize the entity and delay or failure in carrying out the indicated resuscitation. The most important factor of all is time.

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ONE-STAGE SUPRAPUBIC PROSTATECTOMY

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THE value of suprapubic prostatectomy has been established by many years of experience with the operation. Not infrequently, however, accepted procedures are improved and such advances may go unheralded or taken for granted. With the introduction of other surgical procedures for the correction of benign prostatic hypertrophy it seems timely to review suprapubic prostatectomy to see if it has maintained its place in the surgical treatment of this condition.

One-stage suprapubic prostatectomy in itself represents an advance. Many can recall the days of the two-stage operation, and one leader in urology even advocated a three-stage operation at one time. The multiple stage operations doubtless served a useful purpose but they are no longer necessary. With the one-stage operation one avoids long periods of hospitalization and there is less morbidity and fewer complications.

Several factors may be mentioned as having accelerated the adoption of a one-stage prostatectomy. In the past decade or two the increased safety of prostatic surgery has encouraged patients to seek relief earlier. Thus, patients in a younger age group come to us in better general health and before extensive renal damage is present. The introduction and intelligent use of the sulfonamides and antibiotics is another important factor. Before their introduction, urinary sepsis was a major cause of catastrophe in prostatic surgery and there was no satisfactory treatment.

Although it appears paradoxical on first consideration, I believe that transurethral resection increased the safety of one-stage prostatectomy. This was accomplished by providing us with an operation to relieve the small fibrotic prostates and vesical neck contractures, and permitted at least symptomatic relief to the bad risk patient with the larger glands. Furthermore, I believe transurethral resection stimulated a return to open surgery for benign prostatic hypertrophy because of the unsatisfactory results which so often followed resection of the larger glands. Transurethral resection is a useful and valuable operation, but has its definite indications and limitations which should be recognized.

One of the most important factors in advancing one-stage prostatectomy, is an appreciation of the importance of certain details in the preoperative study and management of these patients. We all recognize the value of careful general examinations of the patient, particularly the cardiovascular system, and for many years the importance of blood chemistry and renal function studies has been appreciated. An examination of extreme importance which we routinely employ is the intravenous urogram.[1] We have adopted the following

technic. After a preliminary plain roentgenogram of the abdomen, the intravenous contrast medium is injected, and a 14 by 17 inch film made at intervals of 5, 15, 30 minutes, and one hour. At the time of the 30 minute film an additional 8 by 12 film is made of the bladder, prostate and urethra. Although not a routine procedure, when the urogram is completed one may make an additional bladder film after the patient has voided; this makes visible the amount of residual urine.

By careful study of these films one may determine the renal function, the exact status of the upper urinary tract, the condition of the bladder, and the presence of possibly associated disease such as diverticulum, stone, or tumor. One may also estimate the size and type of the prostate which may even show calculi. Furthermore, one may readily determine the need for preoperative drainage and, in most instances, the appropriate operation may be selected without the need for cystoscopy.

Any patient who presents prompt and normal diodrast excretion with an anatomically normal upper urinary tract does not require preoperative drainage of any type. This conviction applies even in the presence of residual urine. I have repeatedly performed a one-stage prostatectomy in patients with 500 cc. or more of clear, uninfected residual urine, insisting only that the urogram demonstrate a normal upper urinary tract.

In contrast, however, preoperative drainage is essential in those patients whose urograms present delayed diodrast excretion with the hour film showing bilateral hydroureter and hydronephrosis. It should be emphasized that we do not attempt to do an intravenous pyelogram in any patient whose blood urea exceeds 60 mg. per cent as there will be no visualization. However, the blood urea may be within normal limits in a patient whose urogram presents a pronounced bilateral dilation of the upper urinary tract. Such a patient requires preoperative drainage, and affirms the fact that the blood urea alone is not a reliable indication of the status of the obstructed kidneys.

The matter of preoperative drainage deserves special comment. Years ago, and in some instances even today, it was routine practice to place an indwelling catheter in every patient admitted for prostatic surgery. This is unnecessary in most cases, and may actually be detrimental. This procedure is all too often followed by infection, chills, fever, and acute prostatitis. There may also be thrombophlebitis of the periprostatic plexus of veins, the danger of which is immediately apparent. In fact, the apparently simple indwelling catheter may initiate a train of events leading eventually to the death of the patient. Its use should therefore be avoided.

We have condemned the indwelling catheter, but acknowledged the necessity for drainage in certain cases of chronic prostatic obstruction. Trocar cystostomy is recommended for those patients requiring a period of prolonged drainage. This procedure was described by Dr. Lower in 1914; since then we have employed it many times, and a careful study of 400 cases has recently been reported.[2] For the patient with the chronically distended bladder which has resulted in upper urinary tract dilation and renal damage, we feel it is vastly superior to the indwelling catheter. Furthermore, it permits a subsequent

one-stage prostatectomy. This implies that we do not consider trocar cystostomy as a first stage operation, even though the results accomplished are essentially the same.

The technic for trocar cystostomy has been previously described.[2] It is especially applicable to those cases of long standing chronic obstruction, and should be employed only if the bladder is clearly palpable above the symphysis. When indicated, it should be employed as the initial drainage procedure, rather than a subsequent measure after an indwelling catheter has provoked a urinary infection.

According to these principles, we see that the patients fall into two broad categories: the one in which no preliminary drainage is required, and the other which requires prolonged drainage best accomplished by trocar cystostomy. Between these two classifications are the patients with complete urinary retention who require intermittent catheterization until they can be adequately examined in anticipation of operation. In a group of 100 recent consecutive prostatectomies, trocar cystostomy was employed in 11 per cent.

Having discussed the preoperative factors which have contributed to the advancement of suprapubic prostatectomy, let us consider the indications for this operation. I am of the opinion that any patient with severe obstructive symptoms produced by benign enlargement of the prostate which has attained an estimated size of 60 Gm. or more is a candidate for suprapubic prostatectomy. This procedure should be advised provided the patient's general condition is satisfactory, and the presence of adequate renal function has been established. For several years when transurethral resection was advocated, I resected all such patients. While it is possible to do a prostatectomy with the resectoscope, one-stage suprapubic prostatectomy is preferable for the large glands. The mortality is no higher, the morbidity questionably greater, and the late results are more gratifying to the patient and surgeon. I have never regretted advising prostatectomy, but have done resections on a number of patients on whom I wish I had performed prostatectomies. I have also performed prostatectomies on a number of patients who had had previous transurethral resections.

The other important indication for suprapubic operation is the presence of associated disease in the bladder. In a review of 100 recent cases we find that 8 had diverticulectomies, 2 had excision of bladder tumors, and 11 had stones removed from the bladder at the same operation during which the prostate was removed. This, of course, is one of the main advantages of the suprapubic operation over the retropubic; it affords an opportunity for careful inspection of the bladder which occasionally reveals previously unsuspected disease.

There are certain points in the technic of the operation which appear important, although not necessarily new. We have preferred carefully controlled spinal anesthesia. Intravenous fluids are given throughout, and blood is available, although not given routinely.

A midline suprapubic incision is usually employed, although in obese per-

sons a transverse incision is generally chosen in order to facilitate better wound healing. The incision in the bladder is made as high as the peritoneal reflection will allow and I believe it is important to bring the bladder up to the incision to avoid extensive exposure of the perivesical spaces (fig. 1).

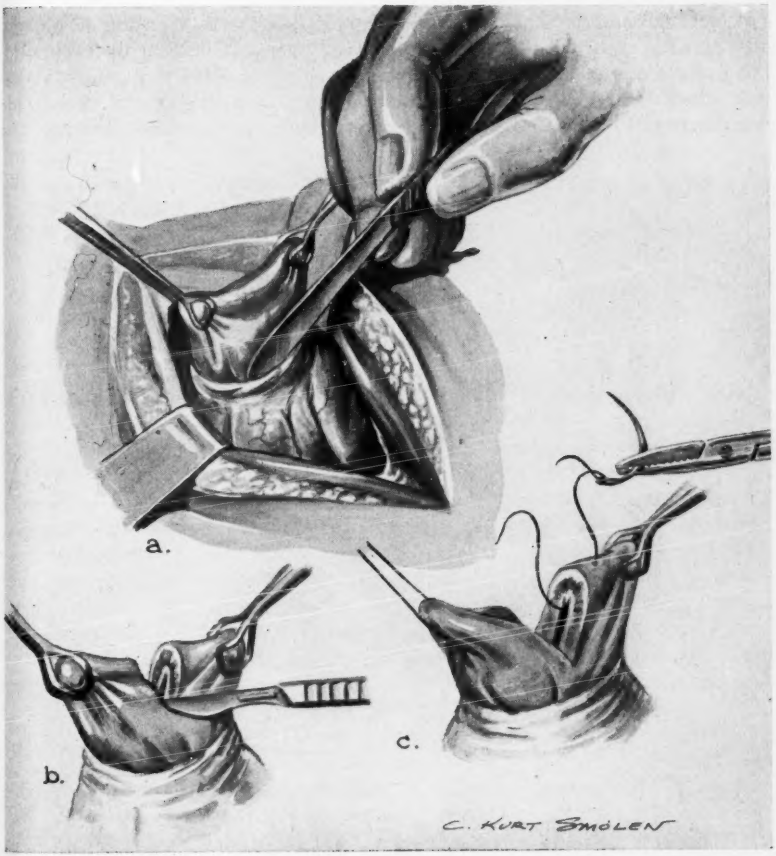

FIG. 1. (a) Bladder drawn up into incision and peritoneal reflection being pressed back. (b) Bladder opened between Allis forceps. (c) Retraction suture being placed deeply through bladder wall. When these are placed on each side, Allis forceps are removed.

Having carefully inspected the bladder to exclude associated lesions, one proceeds to enucleate the hypertrophied portion of the prostate. It is important to recall that only the pars anterior of the prostate is involved in benign pros-

tatic hypertrophy, and the compressed pars posterior forms the so-called capsule of the enlarged gland. Furthermore, the enlargement may be chiefly intravesical or subvesical and, in the latter case, the ureteral orifices may be drawn up out of their normal position, a fact which must be recognized to avoid injury.

The right index finger is introduced into the urethral orifice and the mucosal covering manually ruptured just at the vesical neck at about 11 o'clock and 1 o'clock, the anterior angle between the lateral lobes representing 12 o'clock (fig. 2). One then feels the smooth surface of the enlargement on each side. The mucosa and muscle fibers, when present, are then cleanly cut under vision with scissors in a circular direction completely around the vesical neck. This clean incision I believe to be a major factor in avoiding excessive bleeding.

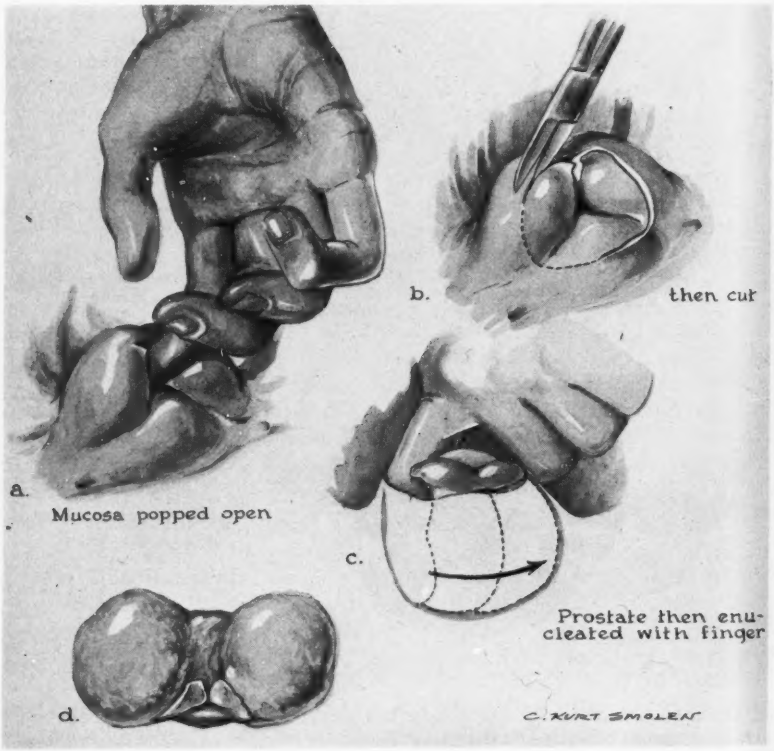

FIG. 2. (a) Drawing designed to show location of breaking through mucosal covering of left lobe of prostate at 11 o'clock position. A similar maneuver exposes the right lobe at 1 o'clock position. (b) Mucosal and muscular covering cleanly incised with scissors around vesical neck. (c) After urethral attachments have been divided as described in text, the prostate is carefully enucleated with right index finger. (d.) As illustrated.

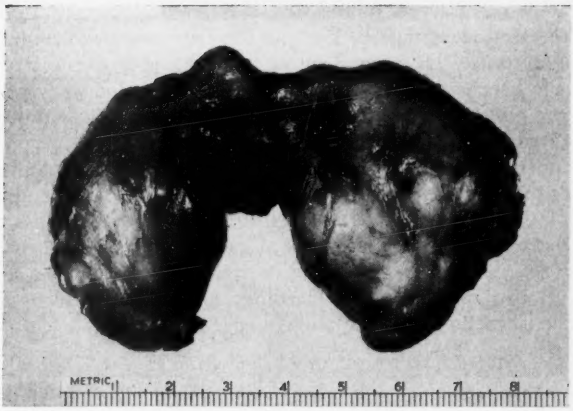

FIG. 3. Photograph of typical prostate removed at operation. Note that lateral lobes are connected by posterior commissure or middle lobe. They fall apart since there is no connection above.

The well lubricated index and middle finger of the left hand is now introduced into the rectum, the patient having been appropriately draped. The rectal fingers serve as a guide and prevent the prostate from being pushed down.

The index finger of the right hand is now introduced into the urethra, the verumontanum is palpated, and the urethral mucosa manually ruptured proximal and lateral to the veru. The cleavage plane is again felt and the urethral mucosa carefully separated down to the apex and then back along the upper margin of the left lateral lobe until the separation joins the original rent made at the vesical neck. By an exactly similar maneuver the mucosal covering of the right lobe is then separated until it joins the original rent made at 1 o'clock. In this manner all mucosal covering and attachments to the hypertrophied gland have been divided. Then, by careful digital enucleation, the smooth hypertrophied prostate is separated from its so-called capsule.

The separation described should not be hurried. I am convinced that painstaking care in this phase of the operation avoids breaking into false cleavage planes which may precipitate excessive bleeding and later complications.

When completely separated, the prostate is carefully lifted from its bed and, in the typical case providing the enucleation has been properly done, it will be in one piece with the two lateral lobes attached to a median lobe or commissure but open above so that it falls apart in butterfly shape (fig. 3). The prostatic fossa is temporarily packed with a hot gauze tape held firmly in place with a ribbon retractor while the operator changes gloves. If this is done in a leisurely manner all significant bleeding usually will have ceased by the time he returns to the operation. The gauze is gently removed from the fossa and any stray mucosal tags which might retard normal healing are trimmed away.

It is rarely necessary to suture any vessels. Occasionally a small spurter will require electrocoagulation, but the majority of cases require no special maneuvers to control bleeding. I never pack the prostatic fossa. Oxycel and gelfoam have been employed in the past, but discarded as unnecessary and because slow absorption produced a "mud" which blocked the urethra and delayed wound healing.

At the operation a No. 24 bag catheter with a 30 cc. balloon is introduced through the urethra. The bag is distended to 25 or 30 cc., depending upon the diameter of the vesical neck. It is then drawn down in such a manner as to lightly compress and invert the vesical neck but *should never be drawn into the prostatic cavity*. To do so prevents the cavity from contracting normally, invites continued and excessive bleeding, and may produce postoperative incontinence if traction has been applied (fig. 4).

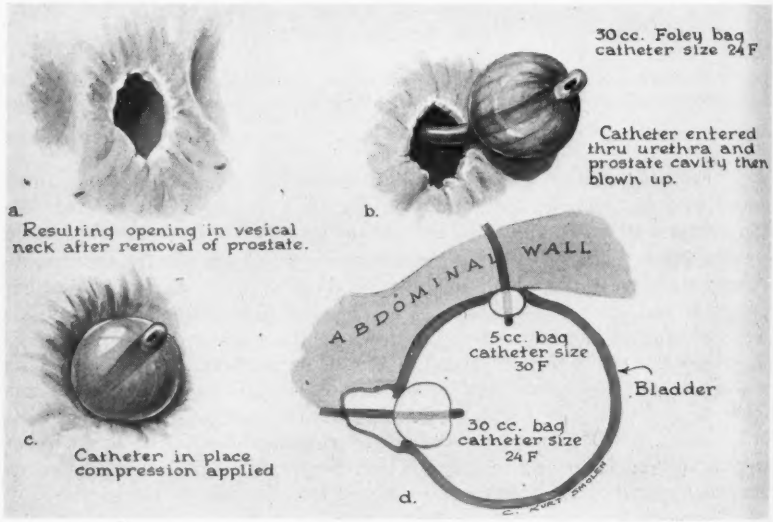

FIG. 4. (a) Appearance of vesical neck looking into prostate cavity after removal of prostate. (b) A No. 24 urethral catheter is introduced and the 30 cc. bag inflated. It is then drawn down *against* the vesical neck as shown (c). (d) Diagrammatic representation of the relative positions of urethral and suprapubic bag catheters when operation is completed. Note that bag of urethral catheter is not in prostate cavity.

After proper bladder toilet, a 30 F. catheter with a 5 cc. bag is placed in the bladder above, and the bladder closed tightly around it. It is usually wise to bring the perivesical fibrofatty tissue together above this as a second layer of suture. A small cigarette drain is placed in the prevesical space and the abdomen closed in layers with interrupted catgut, all layers being closed tightly around the suprapubic tube. Vasectomy is optional. In the study of 100 pa-

tients, vasectomy was performed in 45. There were but two cases of epididymitis in the remaining 55.

The patient is returned to bed and a continuous through and through drip of saline solution is introduced into the urethral catheter and out of the suprapubic tube. This is discontinued as soon as evidence of active bleeding has disappeared. The suprapubic tube is regarded as merely a safety valve against possible excessive bleeding and should be removed as soon as the danger of bleeding has passed. In the majority of cases the suprapubic catheter is removed 36 to 48 hours following operation. Early removal is encouraged before a sinus tract forms and while the tissues are sufficiently flexible to fall together and heal by primary union. By following this principle, persistent suprapubic fistulae have become a rarity and the scar which remains resembles that subsequent to a clean laparotomy.

The prevesical drain is removed 24 hours following the removal of the suprapubic tube and the urethral catheter as a rule is removed 7 days later. Thus the patient is usually voiding normally 9 to 10 days after operation and if the situation continues normal for a day, he is permitted to go home.

Although in these cases we do not encourage immediate ambulation, bed exercises are instituted from the time the operation is completed. Especially important are deep breathing and regular exercise of the leg and calf muscles. The patient is permitted to sit upright in bed and his position frequently changed. If he is an habitual smoker, this habit may be resumed promptly and a strong pipe assures a speedy recovery. For such patients the operation is an incidental experience.

As soon as the suprapubic tube has been removed, the patient is allowed to get out of bed any time he desires and is encouraged to do so. The majority seize this opportunity because of the toilet privileges and I have no doubt that this is a factor in preventing troublesome postoperative constipation.

In order to visualize and illustrate the change occurring in the suprapubic operation for prostatic hypertrophy I have studied 100 consecutive patients whom I have recently operated upon with the enumerated principles in mind and compared or contrasted their cases with similar ones having been operated upon at the Clinic 25 years ago. This seems like a convenient period and is of special interest to me, since it encompasses my own career in medicine. I was particularly concerned with the method of preoperative preparation, the number of two-stage operations done in the past, the postoperative days allocated for convalescence, and the incidence of significant complications. Mortality statistics were also tabulated in this review. This study reveals the following interesting facts.

Twenty-five years ago the average hospital stay before the operation was 10.6 days, with a minimum of 3, and a maximum of 58. Of the recent cases, the average was 2.8 days, with a minimum of 1, and a maximum of 12. Following operation, the average stay 25 years ago was 30 days, with a minimum of 11 and a maximum of 106. The recent patients were hospitalized for an average of 17.7 days, with a minimum of 10, and a maximum of 74.

All patients of the older series wore indwelling catheters before operation and it is significant that 64 per cent of these had fever recorded as 100 F. or higher. Four of the recent patients were admitted to the hospital wearing indwelling catheters, and they represent the only cases so handled.

The operative mortality in the older series was 12 per cent, while among recent patients it was 1 per cent.

In recording these statistical figures which are summarized in table 1, it is not intended that one should draw absolute conclusions. However, I believe they indicate that significant improvements have been made in doing suprapubic prostatectomy, and that it has retained and improved its position as a method for the surgical treatment of benign prostatic hypertrophy.

Table

COMPARABLE SERIES **Suprapubic Prostatectomy**		
	Present Series	25 years ago
Average preoperative hospital days	2.8	10.6 (64% with fever)
Average postoperative hospital days	17.7	31
Indwelling catheter	4%	100%
2 stage prostatectomy	0	12%
Trocar cystostomy	11%	4%
Operative mortality	1%	12%

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MARGINAL ULCER FOLLOWING GASTRIC RESECTION FOR BENIGN GASTRIC ULCER

A Case Report

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THE development of a marginal ulcer following gastric resection of a *gastric* ulcer is unusual. Balfour, cited by Bockus,[1] reported that marginal ulcer occurred 20 times more frequently after operations for duodenal ulcer than after surgery for gastric ulcer. Kiefer[2] obtained follow-up studies on 49 patients with gastric ulcers subjected to subtotal gastrectomy, and found no evidence of recurrence in any of the patients. Of 146 patients with duodenal ulcer and 27 patients with jejunal ulcer subjected to gastric resection, 6 or 3.4 per cent developed marginal ulceration as proved at subsequent operations. Bockus[1] reported that marginal ulceration rarely occurred even after a gastrojejunostomy was performed for gastric ulcer. Ranson[3] followed 188 patients who underwent gastric resection for gastric ulcer and found that only 4 had developed marginal ulcers. In at least 2 and possibly 3 of the patients the antrum was not removed, a Finsterer operation having been performed. The presence of the antrum, with the continued secretion of the antral hormone as shown by Dregstedt, can predispose to the development of an anastamotic ulcer. In none of the 4 patients with a marginal ulcer was a Bilroth I type of procedure done.

The occurrence of a marginal ulcer is dependent on gastric acidity and the presence of free HCl, just as any peptic ulcer. Klein et al[4] found that immediate postoperative anacidity was present in 77 per cent of patients with gastric ulcer following resection, and in only 38 per cent of patients with duodenal ulcer who had resections done. Kiefer[2] measured gastric acidity in 30 patients with gastric ulcer subjected to resection and found a small amount of free HCl in only 3 of the 30 patients.

From the pathologic physiology of peptic ulcer, it is logical that marginal ulceration should occur less frequently after operations for gastric ulcer than following surgery for duodenal ulcer. Levin et al,[5] and many others, have shown that patients with duodenal ulcer are "hypersecretors," have increased gastric acidity, and continued nocturnal secretion of hydrochloric acid. Conversely, Levin et al[6] have shown that patients with gastric ulcer have normal or subnormal gastric acidity. One would expect fewer occurrences of marginal ulcer following operations in the group of patients with low acid values (gastric ulcer group) than in the group evidencing high acidity (duodenal ulcer group).

The location of the anastamosis between the stomach and the small bowel is another factor in the development of an anastamosis ulcer. Gastroileostomies,[7,8] performed mistakenly, show a high incidence of marginal ulcer. The lower the anastamosis is made between the stomach and the small bowel, the greater the likelihood of a marginal ulcer; conversely, the higher in the small intestine the anastamosis is made, the less likely the development of marginal ulcer. The alkaline duodenal contents have the greatest chance to neutralize the acid gastric chyme with the high anastamosis. Consequently, one would not expect an anastamotic ulcer to develop following a Bilroth I procedure done for gastric ulcer.

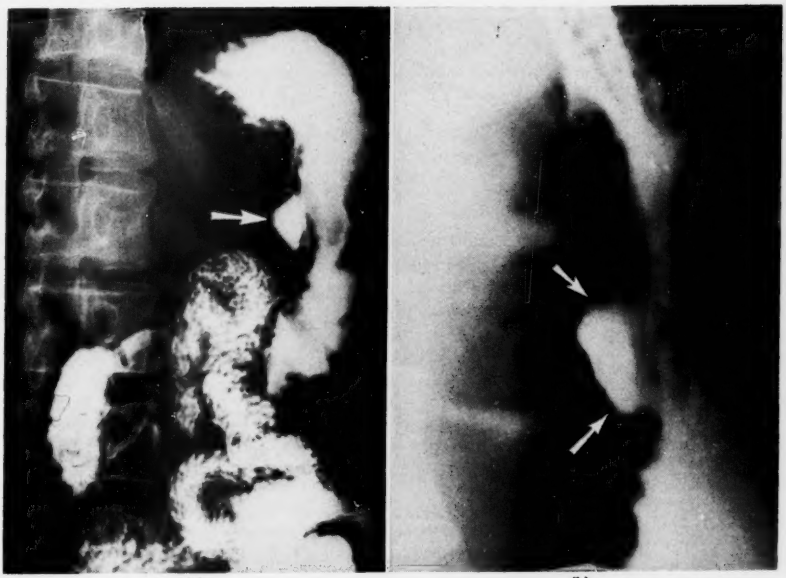
We are presenting the case of a patient who had an 80 per cent gastric resection with a Bilroth I procedure for a large penetrating gastric ulcer on the posterior wall; he subsequently developed a marginal ulcer that healed promptly on intensive medical treatment.

Report of a Case[9]

A 66 year old man came to the Cleveland Clinic September 11, 1950, with the complaint of epigastric pain relieved only occasionally by food and usually requiring "pain pills" of 10 months' duration. He had lost 12 pounds in weight. Complete examinations elsewhere, including gastrointestinal roentgen examinations, had been entirely negative in February and April.

On general physical examination, his weight was 112 pounds, and his blood pressure 100/60. No masses were present in the abdomen, and general physical examination was noncontributory. Laboratory studies showed the hemoglobin to be 12.5 Gm., white blood cell count 7,450 per cubic mm., and stools negative for blood. Gastric analysis with alcohol as a stimulant showed 12 units of free HCl and 22 units of total acidity. Urinalysis, bromsulphalein liver function test, serum proteins, serology, blood sugar and serum amylase were either normal or negative. Roentgenograms of the chest, sinuses, gallbladder and colon were negative except for left maxillary sinusitis and osteoarthritis of the spine. However, x-ray examination of the stomach revealed a large ulcer measuring 3 cm. in diameter on the posterior aspect of the stomach. There was slight indentation of the margins, suggesting possible meniscus sign. On gastroscopic examination the ulcer was visualized midway between the lesser and greater curvatures; the edges of the ulcer did not appear sharply delineated, and the base was filled with dirty, gray material and some old blood. The gastroscopic appearance suggested possible malignancy (fig. 1a and b).

The location of the ulcer on the posterior wall, the atypical history with relatively recent onset of symptoms, the low gastric acidity, the suggestive meniscus sign on roentgen study, the size and location of the ulcer, and the gastroscopic appearance all indicated the possibility of malignancy. Consequently, the patient was advised to undergo surgery, and was operated upon on September 25, 1950. At operation, a gastric ulcer on the posterior wall midway between the greater and lesser curvatures was found, with penetration into the pancreas. A gastric resection, with a Bilroth I procedure, was done, the ulcer bed being left on the pancreas. Eighty per cent of the stomach, including the antrum and pylorus, was resected, and the duodenum was anastamosed to the resected end of the stomach (fig. 2).



(a) (b)

FIG. 1. (a) Large gastric ulcer on lesser curvature and posterior wall; seen on survey film. (b) Spot film of large gastric ulcer. Note some irregularity of the proximal border of the ulcer (2 arrows) and suggestions of overhanging edges at the interior margin (1 arrow) suggesting possibility of malignancy.

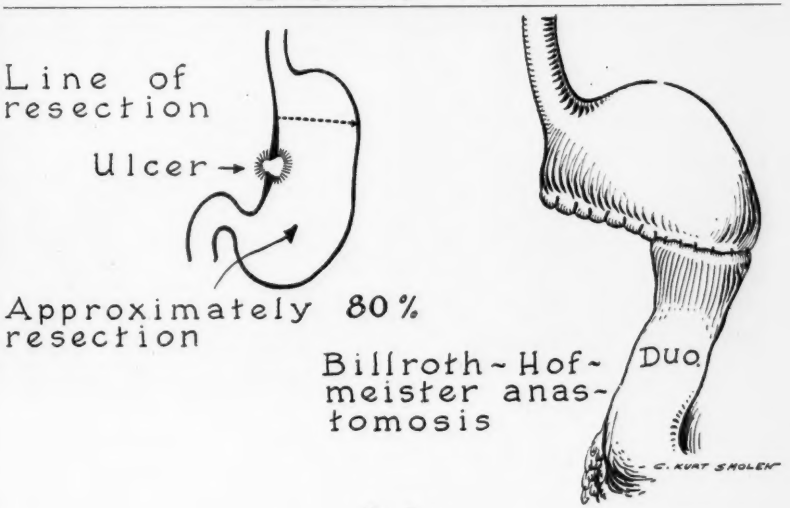


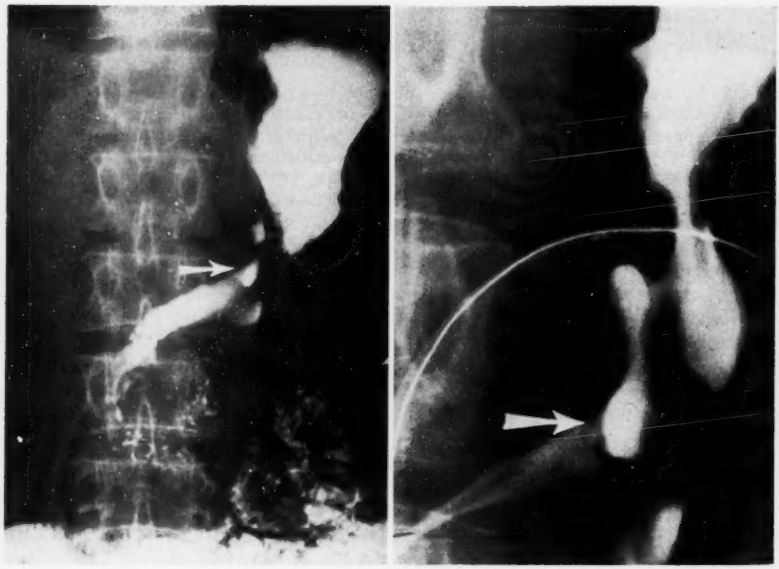
FIG. 2.

Pathologic examination revealed the surgical "perforation" of the stomach 2 cm. in size where the ulcer bed had been left behind. Microscopic sections showed that the ulcer margin had typical zones of peptic digestion. There was no evidence of neoplasm and no atypical cells were seen.

The patient made an uneventful recovery, and was discharged from the hospital October 7, 1950. He returned 5 months later. At that time he had no ulcer distress, but demonstrated mild dumping symptoms with palpitation and nausea 10 to 15 minutes after eating.

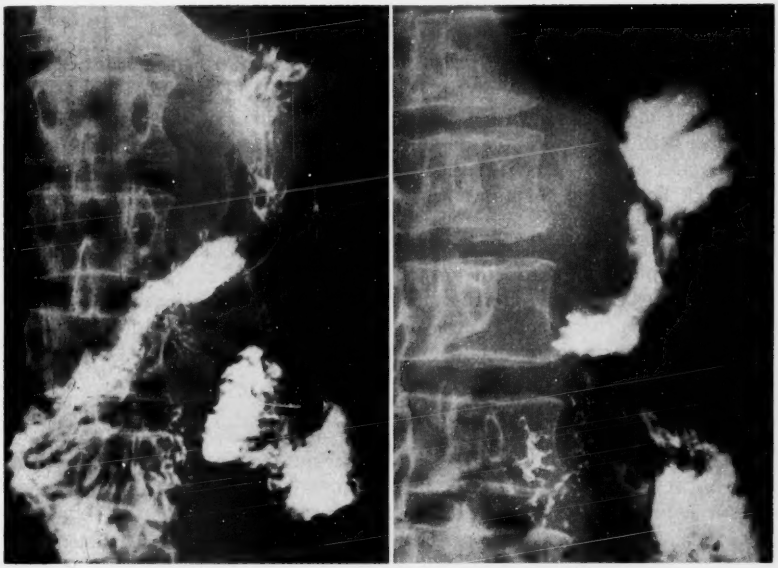
He returned again on September 20 and reported that he had experienced ulcer-type distress, commencing before meals and relieved by food, following a sore throat six weeks previously. He had neither vomited nor noted tarry stools. Roentgenograms of the stomach showed the distal two-thirds of the stomach had been resected and the remaining portion anastamosed to the duodenum. Immediately distal to the anastamosis, an ulcer crater approximately 1 cm. in size was visualized and appeared to lie in the duodenum or along the line of the anastamosis (fig. 3a and b).

Because of the unusual occurrence of marginal ulcer following an 80 per cent resection for *gastric* ulcer, particularly a Bilroth I procedure in which the gastric acid is neutralized immediately on entering the duodenum, and because of the low gastric



(a) (b)

FIG. 3. (a) Survey film showing marginal ulcer (arrow). The collection of barium above the ulcer is probably in a pocket caused by spasm from the ulcer. (b) Spot film showing the marginal ulcer.



(a) (b)

FIG. 4. (a) Large film showing no evidence of marginal ulcer. (b) Another view showing no evidence of marginal ulcer. Repeated films on progress visits failed to demonstrate any sign of previously described ulcer.

acidity of the patient, we elected to treat the marginal ulcer medically. He was given a bland diet, allowing meat, with food or milk every two hours on the even hours, and was asked to take two drams of an aluminum hydroxide preparation every two hours on the odd hours. Coffee, tea and alcohol were forbidden, and an anti-cholinergic (*Prantal-100 mg. qid.) and vitamin B capsules were prescribed.

The patient followed the suggested hourly ulcer schedule and returned 5 weeks later. He reported immediate relief from his ulcer distress on this regimen and subsequent freedom from symptoms. On progress roentgen examination the previously observed ulcer crater could not be visualized. At this time the patient's diet was enlarged to to include fresh fruits and vegetables, but he was kept on the hourly ulcer schedule with food or milk on the even hours and anti-acids on the odd hours.

He returned again two-and-one-half months later and reported continued freedom from ulcer distress. Roentgen examination of the stomach again showed a normal functioning gastroduodenostomy with no evidence of an anastamotic ulcer. At this time he was placed on a modified ulcer program with a liberal diet—milk two hours after meals and anti-acids one hour after meals and at bedtime. He had remained free of ulcer distress when last contacted July 8, 1952 (fig. 4a and b).

Kindly supplied by Schering Corporation.

Summary

It is rare for a marginal ulcer to develop following a gastric resection for *gastric* ulcer.

The case of a patient with a large posterior wall benign gastric ulcer has been presented. At operation the ulcer was found to have penetrated the pancreas and an 80 per cent gastric resection with a Bilroth I procedure was performed. Pathologic examination showed the ulcer to be benign. Approximately one year later the patient developed typical ulcer symptoms and a large marginal ulcer was demonstrated by roentgen examination. He was placed on intensive medical treatment for the ulcer, and progress examinations five weeks and three-and-three-fourths months later showed the ulcer to have healed completely. This case demonstrates the fact that marginal ulceration may heal with intensive medical treatment.

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DIAGNOSIS AND TREATMENT OF THYROIDITIS WITH SPECIAL REFERENCE TO THE USE OF CORTISONE AND ACTH

GEORGE CRILE, JR., M.D. and R. W. SCHNEIDER, M.D.

THE 2 commonest types of thyroiditis are (1) subacute or giant cell thyroiditis and (2) struma lymphomatosa or Hashimoto's disease. Variants of the latter type of thyroiditis are common, but in the absence of the characteristic oxyphilia of the cells we classify them as lymphoid thyroiditis, not as true struma lymphomatosa.

Clinical Features of Subacute Thyroiditis

Subacute thyroiditis may manifest itself in a number of different ways. In its most fulminating form, the onset is quite sudden and is associated with severe pain in the thyroid, a high temperature and a marked systemic reaction. Frequently the patients are prostrated by their illness and narcotics may be required to control the pain. More often the disease is milder, is associated with a low-grade temperature and pain in the region of the thyroid which radiates up to the ears and may be interpreted by the patient as a sore throat.

In the chronic form of the disease, there may be little or no pain and tenderness, but the hard enlargement of the thyroid causes an unpleasant sensation of pressure or choking and the hardness of the gland may simulate adenoma or carcinoma of the thyroid.

Subacute thyroiditis usually involves both lobes of the thyroid but may originate on one side and slowly cross the isthmus and involve the other at a later date. The symmetrical involvement of the entire lobe characterizes the process even when only 1 lobe is involved and differentiates it from adenoma and carcinoma which usually are localized to only a portion of the lobe. A high sedimentation rate and a low uptake of radioactive iodine characterize subacute thyroiditis. In questionable cases, the diagnosis can be confirmed by Silverman needle biopsy of the thyroid.[1]

Conventional Treatment of Subacute Thyroiditis

For many years, we have employed x-ray therapy as standard treatment for subacute thyroiditis, giving 600 to 1000 r. This amount of radiation produces no permanent impairment of thyroid function and results in prompt relief of pain and tenderness, subsidence of the systemic reaction and, within a week or 2, in a striking diminution in the size and hardness of the thyroid. Even in the chronic cases, the process resolves promptly in response to x-ray therapy. There is no indication for surgical removal of a thyroid involved with this type

of inflammatory process, because the disease is self-limited and responds well to conservative therapy. It is said that thiouracil and methyl thiouracil also are effective.[2]

ACTH and Cortisone in the Treatment of Subacute Thyroiditis

Although x-ray therapy is a satisfactory means of treating subacute thyroiditis, there are some cases in which the symptoms are so severe that even quicker relief of symptoms is desirable, and there are others which for diagnostic reasons (because of the suspected possibility of the presence of cancer) it is desirable to obtain a definitive clinical response as early as possible. In such cases, ACTH or cortisone produce a prompt remission of symptoms and resolution of the hard mass in the thyroid. The first patients so treated that we have seen were in the clinic of Doctor Wineblad in Copenhagen where ACTH was being used. Recently we have had occasion to employ ACTH and cortisone in 2 patients with subacute thyroiditis, with excellent immediate results. Although recurrences are to be anticipated following short courses of therapy, these may be prevented by the simultaneous administration of x-ray therapy. Symptoms are relieved within 4 hours of the first dose of steroids and striking changes in the size and consistency of the thyroid occur within 48 hours.

Case Reports

Case 1. The patient was a married woman 29 years of age, who complained of a sore throat and painful swallowing of 6 weeks' duration. Just before the onset of the sore throat, she had had "virus influenza" associated with a high temperature. The "sore throat" did not respond to treatment with Terramycin, and there was a slight daily elevation of temperature.

Examination showed the thyroid to be diffusely enlarged to about twice its normal size, hard and exquisitely tender. The sedimentation rate was elevated to 1.9 mm. per minute, and a tracer dose of radioactive iodine showed no uptake of iodine in the thyroid. A needle biopsy taken with the Silverman needle showed typical subacute thyroiditis with giant cell reaction.

The patient was given 25 mg. of cortisone 4 times daily for 2 days. She felt greatly improved as soon as therapy was started and the pain and tenderness in the thyroid disappeared. These changes were noted within 6 hours of the first dose of cortisone. The dosage was then decreased to 25 mg. twice daily, but within 4 days symptoms recurred and the gland which had shrunk to two-thirds of its original size remained of the same size and consistency. The dose of Cortisone was again increased to 100 mg. daily, and again the symptoms disappeared promptly, the patient felt well, and the gland diminished further in size and became softer. At this point, 2 x-ray treatments of 150 r each were given to the thyroid area. Twelve days later (23 days after the patient was first seen) the thyroid was barely palpable, the patient had gained 7 pounds, was feeling well and had no residual pain or tenderness in the thyroid area.

Case 2. The patient was a married woman 48 years of age, who complained of pain in the right side of the neck radiating up to the right ear. The onset was gradual, 3

months before examination at the Clinic, and was associated with a low-grade fever. She had been given 2 x-ray treatments to the right lobe of the thyroid, with improvement of the symptoms; the pain and tenderness then shifted to the left side of the neck and 2 more x-ray treatments were given. Three weeks before entry she was given a course of penicillin in an attempt to control the fever. Two days previous to entry, she developed severe hives as a result of the penicillin therapy. Benadryl had failed to relieve the itching.

Physical examination showed an uncomfortable woman with severe urticaria, a temperature of 99.6 and an exquisitely tender thyroid gland. She was so uncomfortable that it was felt desirable to have her admitted to the hospital, where she was given 80 mg. of ACTH every 6 hours intravenously. The itching and the pain in the thyroid disappeared within 2 hours of the time the ACTH was started. The next day the eruption was almost gone and the thyroid was much less swollen and much softer. The thyroid was no longer painful and the gland, which on the day before had been so exquisitely tender that it could not be palpated, was no longer tender. After 48 hours of treatment, the patient was so much improved that she was sent home on decreasing doses of cortisone.

Two other patients with subacute thyroiditis have been treated with 75 to 100 mg. of cortisone daily with similar prompt remission of the signs and symptoms of subacute thyroiditis.

Clinical Features of Struma Lymphomatosa

Struma lymphomatosa or its variants loosely grouped under the term "lymphoid thyroiditis" occur predominantly in women. True struma lymphomatosa usually occur in women beyond the age of 40, but lymphoid thyroiditis may occur in young women in the twenties or even in children. Enlargement of the thyroid is frequently noted during or following childbirth. The leading symptom is usually a painless, symmetrical enlargement of the thyroid which sometimes gives unpleasant sensations of pressure. Sometimes the enlargement is rapid and the gland may grow to 4 or 5 times its normal size within a period of a few months. More commonly the onset is gradual, associated with no significant symptoms, and is characterized by a firm, rubbery consistency and a symmetrical involvement of both lobes. Irregular bosselations frequently cause the examiner to make a diagnosis of adenomatous goiter. Often there is a mild hypothyroidism and the basal metabolism is usually below 0. Occasionally myxedema occurs. In all symmetrical, firm, nodular-feeling goiters, when both lobes are involved, struma lymphomaotsa must be suspected, and even more so if the basal metabolism is less than 0. The diagnosis can be confirmed by needle biopsy.

Treatment

Lymphoid thyroiditis responds specifically to the administration of large doses of desiccated thyroid. The rationale of this therapy is to put the thyroid

completely at rest. For this reason, small doses are ineffective and doses of at least 2 gr., preferably 3 gr., of desiccated thyroid daily are required. Patients usually tolerate thyroid well if the dose is increased gradually from 1 gr. to 3 over a 3 weeks' period. The enlargement of the thyroid usually disappears completely after 1 or 2 months of thyroid therapy, but may recur if therapy is discontinued. X-ray therapy, in doses of 1500 to 2000 r, may also be of value in lymphoid thyroiditis, but since the disease responds so specifically to desiccated thyroid neither x-ray nor surgery is indicated.

True struma lymphomatosa may be more resistant to treatment with desiccated thyroid and may also be resistant to x-ray therapy. Nevertheless, 90 per cent of the cases of struma lymphomatosa which we have observed have responded satisfactorily to treatment with large doses of desiccated thyroid, x-ray therapy in doses of 1500 to 2000 r, or a combination of both types of therapy. Usually the enlargement disappears almost completely, but the consistency of the thyroid remains firm due to the fibrosis which is present in the gland. In this respect, the results of treatment differ from those following the treatment of lymphoid thyroiditis, in which the consistency of the thyroid tends to return to normal.

Case 3. The patient is a married woman 46 years of age, who had had a thyroidectomy at another hospital in July of 1949. For the past 3 months, she had noticed a rapid recurrence of the goiter and a sensation of choking.

Examination showed a large, hard recurrence of the goiter involving both lobes and the isthmus and with a tiny nodule 1 cm. in diameter palpable in the midline. A needle biopsy of the thyroid was taken, and it showed typical struma lymphomatosa. Sections made at the time of the original operation were reviewed and showed the same changes. A tracer of radioactive iodine showed 62 per cent uptake in 19 hours. Basal metabolism was plus 16 per cent.

The patient was given desiccated thyroid, grains 3 daily, in an attempt to put the thyroid at rest, but after 2 months there was only slight diminution in the size of the gland. The patient was then given roentgen therapy, a total dosage of 2400 r. Two months later the thyroid had diminished further in size and its estimated weight was now 80 Gm. The little midline nodule had disappeared. The left lobe was definitely smaller. The patient continued to take desiccated thyroid, gr. 2 daily, and 2 months later the thyroid enlargement was no longer visible nor was any thyroid tissue palpable except in the right lobe. Here there was a hard mass of thyroid tissue estimated to weigh about 25 Gm. The possibility of the presence of an adenoma was considered. The patient was feeling well, and had no symptoms of thyroid imbalance or of local discomfort.

Cortisone and Desiccated Thyroid in the Treatment of Struma Lymphomatosa

There are occasional cases of struma lymphomatosa which do not respond dramatically either to x-ray therapy or the administration of large doses of desiccated thyroid. We recently observed such a case, in which a dramatic response in the size and consistency of the thyroid followed the administration of cortisone and large doses of desiccated thyroid.

Case 4. The patient was a woman 54 years of age, who was referred with a diagnosis of nodular goiter with hyperthyroidism and rheumatic heart disease. Propyl thiouracil in doses of 50 mg. three times daily had been given for several weeks without relief of the symptoms. She stated that she had noted no unusual nervousness and had not lost weight. She had had a progressive enlargement of the thyroid during the past 2 years.

Examination showed evidence of rheumatic heart disease with aortic stenosis and insufficiency and mitral stenosis and insufficiency. The pulse rate was 92 and blood pressure 146/70. There was no evidence of cardiac decompensation. The thyroid was enlarged and nodular, with an estimated weight of 75 Gm. The basal metabolism was minus 1 per cent and there was no clinical evidence of hyperthyroidism. Since we could not establish the presence of hyperthyroidism, no treatment was advised at this time.

Eighteen months later, the patient returned, complaining that the thyroid was continuing to enlarge and had become tender. At this time the possibility of struma lymphomatosa was considered, and needle biopsy confirmed its presence. In view of the patient's cardiac status, it was thought inadvisable to give large doses of desiccated thyroid and she was given 1 grain of desiccated thyroid daily. This she tolerated poorly, and thought that it made her heart worse. In view of the fact that the thyroid took up 43 per cent of a tracer dose of radioactive iodine, it was decided to attempt treatment with radioactive iodine and 8 mc. was given. The patient felt that this treatment made her thyroid more tender and that it actually continued to enlarge.

Three months later, she was given a course of x-ray therapy, approximately 2000 r, and a second needle biopsy of the thyroid was taken which confirmed the presence of struma lymphomatosa. Five weeks after the x-ray therapy, the thyroid seemed to be still larger. It was now estimated to weigh over 100 Gm. and was easily visible. 25 mg. of cortisone was given 4 times daily for 5 days, 3 times daily for 2 days, twice daily for 2 days and once daily for 2 days. At the same time desiccated thyroid was started in doses of gr. 1 daily for 1 week, gr. 2 daily for 1 week, then gr. 3 daily. The patient noticed that the tenderness of the thyroid disappeared as soon as the cortisone was started and that the gland diminished steadily in size during the cortisone and thyroid treatment. Within a month it had decreased to less than a half of its original size, and was no longer visible. The patient was gratified with the absence of symptoms.

The effects of cortisone on struma lymphomatosa may be only transitory if large doses of desiccated thyroid are not given at the same time. In one such case the gland diminished to about half of its original size in 10 days but grew again as soon as therapy was discontinued. If desiccated thyroid is given along with cortisone the improvement which cortisone produces in the size and consistency of the thyroid may be maintained.

Summary

1. Subacute thyroiditis and the lymphoid types of thyroiditis including Hashimoto's disease are amenable to medical treatment, and surgical intervention rarely is required.

2. ACTH and/or cortisone produce a prompt and complete remission of the symptoms of subacute thyroiditis and cause rapid regression in the size and hardness of the thyroid swelling in both subacute thyroiditis and the lymphoid types of thyroiditis.

3. X-ray therapy is beneficial to both subacute thyroiditis and the lymphoid types of thyroiditis, but is not often required in the latter because the process usually can be well controlled by the administration of large doses of desiccated thyroid.

4. Needle biopsy of the thyroid has proved valuable in confirming the diagnosis of thyroiditis and in avoiding operation in patients whose problems are amenable to conservative therapy.

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ANNOUNCEMENTS

Annual Lower Lecture

The Fifteenth Annual William E. Lower Lecture will be given at the Academy of Medicine in Cleveland on Friday, November 21, at 8:30 p.m. The lecturer this year will be Dr. Herrman L. Blumgart. Dr. Blumgart is Professor of Medicine at the Harvard Medical School and Director of Medical Research and Physician-in-Chief at the Beth Israel Hospital, Boston. He is an eminent teacher and investigator and an unusually gifted speaker. His studies of the correlation of the clinical manifestations of coronary heart disease with the pathologic findings in the heart comprise one of the most important recent contributions in the field of cardiology. His subject will be "The Pathologic Physiology of Coronary Heart Disease."

Dr. Cyrus C. Sturgis, Professor of Medicine and Director of the Simpson Memorial Institute, University of Michigan, will be the second annual Physician-in-Chief pro tempore on December 18, 19 and 20, 1952. During his tenure, Dr. Sturgis will devote his entire time to the teaching program of the Fellows in Medicine. A schedule of daily clinics, lectures, and seminars has been arranged. Members of the medical profession are cordially invited to attend.

American College of Physicians Postgraduate Course

A Postgraduate Course on "Pathology and Pathologic Physiology in Internal Medicine" will be given at the Clinic under the auspices of the American College of Physicians from February 16 to February 21, 1953. The course will place emphasis on pathologic anatomy and current concepts of pathologic physiology in systemic disease. The principal objective will be to stress the relationship between pathology, pathologic physiology and clinical diagnosis and treatment. The major subjects to be presented will be in the fields of cardiovascular and renal disease, pulmonary disease, gastroenterology, hematology, endocrinology, and metabolic diseases. The course will include lectures, clinical demonstrations, pathology conferences, and question and answer panels.

Tuition fees will be $30.00 for members of the American College of Physicians and $60.00 for nonmembers. Application should be made directly to Mr. E. R. Loveland, Executive Secretary, The American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa.

A complete program will be published in the January issue of this *Quarterly*.

RECENT PUBLICATIONS BY MEMBERS OF THE STAFF

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CLEVELAND CLINIC QUARTERLY—Volume 19—1952

THE FRANK E. BUNTS INSTITUTE

Announces the following Postgraduate Continuation Courses for October 15 and 16, and for October 29 and 30, 1952.

SURGERY OF THE ABDOMEN

Tentative Program

Wednesday, October 15, 1952

8:00-9:00 a.m.	Registration	
	Morning Session	R. S. DINSMORE, M.D., Presiding
9:00 a.m.	Opening Remarks	R. S. DINSMORE, M.D.
9:05 a.m.	Appraisal of the Cardiac Risk in Abdominal Surgery	A. C. ERNSTENE, M.D.
9:25 a.m.	Anesthesia in Surgery of the Abdomen	D. E. HALE, M.D.
9:45 a.m.	The Abdominal Incision	S. O. HOERR, M.D.
10:00 a.m.	Transfusions in Surgery of the Abdomen	R. B. TURNBULL, JR., M.D.
10:20 a.m.	Intermission	
10:30 a.m.	The Role of Esophagoscopy in Surgery of the Abdomen	H. E. Harris, M.D.
10:50 a.m.	Abdominal Pain of Genitourinary Origin	C. C. HIGGINS, M.D.
11:10 a.m.	The Ovaries and the General Surgeon	J. S. KRIEGER, M.D.
11:30 a.m.	The Surgical Treatment of Hernia	A. H. ROBNETT, M.D.
11:50 a.m.	Surgery of the Adrenal Glands	E. F. POUTASSE, M.D.
12:10 p.m.	Luncheon—Courtesy Bunts Institute	
	Afternoon Session	GEORGE CRILE, JR., M.D., Presiding
2:00 p.m.	Treatment of Duodenal Ulcer	GEORGE CRILE, JR., M.D.
2:20 p.m.	The Problem of Gastric Ulcer	S. O. HOERR, M.D.
2:40 p.m.	Cancer of the Stomach	C. H. BROWN, M.D.
3:00 p.m.	Gastroscopy and Gastric Diagnosis	H. R. ROSSMILLER, M.D.
3:20 p.m.	Lesions at the Diaphragm	D. B. EFFLER, M.D.
3:50 p.m.	Panel—Postoperative Complications	R. S. DINSMORE, M.D. (Moderator) J. E. Dunphy, M.D. (Guest), D. M. Glover, M.D. (Guest) George Crile, Jr., M.D., S. O. Hoerr, M.D.
6:00 p.m.	Dinner—Courtesy Bunts Institute	
7:30 p.m.	Evening Lecture—Acute Postoperative Pancreatitis	J. E. DUNPHY, M.D. (Guest)

Thursday, October 16, 1952

	Morning Session	S. O. HOERR, M.D., Presiding
9:00 a.m.	Acute Intestinal Obstruction, Large Bowel	R. B. TURNBULL, Jr., M.D.
9:20 a.m.	Acute Intestinal Obstruction, Small Bowel	A. H. ROBNETT, M.D.
9:40 a.m.	The Pathologist Looks at Rectal Polyps	J. B. HAZARD, M.D.
10:00 a.m.	Management of Cancer of the Rectum	R. B. TURNBULL, JR., M.D.
10:20 a.m.	Intermission	
10:30 a.m.	Management of Advanced or Recurrent Cancer of the Colon	J. E. DUNPHY, M.D. (Guest)
10:50 a.m.	Ulcerative Colitis	E. N. COLLINS, M.D.

11:10 a.m.	Ileostomy with Skin Graft (moving picture)	Robin Anderson, M.D.
11:30 a.m.	Panel—Surgery of the Colon	George Crile, Jr., M.D. (Moderator) J. E. Dunphy, M.D. (Guest), R. B. Turnbull, Jr., M.D. E. N. Collins, M.D.
12:15 p.m.	Luncheon	
	Afternoon Session	R. B. Turnbull, Jr., M.D., Presiding
2:00 p.m.	Indications for Cholecystectomy	R. S. Dinsmore, M.D.
2:20 p.m.	Management of Acute Cholecystitis	J. E. Dunphy, M.D. (Guest)
2:50 p.m.	Chronic Recurrent Pancreatitis	George Crile, Jr., M.D.
3:10 p.m.	Operative Cholangiography (moving picture)	S. O. Hoerr, M.D.
3:30 p.m.	Technical Problems in Splenectomy	R. S. Dinsmore, M.D.
3:50-5:00 p.m.	Panel—The X-ray in Diagnosis of Abdominal Surgical Diseases	S. O. Hoerr, M.D. (Moderator) J. E. Dunphy, M.D. (Guest) C. R. Hughes, M.D., George Crile, Jr., M.D. R. B. Turnbull, Jr., M.D., E. N. Collins, M.D.

MANAGEMENT OF COMMON DERMATOLOGIC PROBLEMS

Tentative Program

Wednesday, October 29, 1952

8:30-9:00 a.m.	Registration	
	Morning Session—E. W. Netherton, M.D., Presiding	
9:00 a.m.	Opening Remarks	F. A. LeFevre, M.D.
9:10 a.m.	Atopic and Contact Dermatitis	E. W. Netherton, M.D.
9:30 a.m.	Seborrheic Dermatitis	G. H. Curtis, M.D.
9:50 a.m.	Fundamentals of Dermatologic Therapy	E. W. Netherton, M.D.
10:10 a.m.	Surgical Procedures and their Indications in Varicose Ulcers and Stasis Dermatitis	A. H. Robnett, M.D.
10:30 a.m.	Intermission	
10:45 a.m.	Present Day Concepts of the Management of Syphilis	A. C. Curtis, M.D. (Guest)
11:30 a.m.	Use and Abuse of Cortisone and ACTH in Management of Common Dermatoses	J. R. Haserick, M.D.
11:50 a.m.	Treatment of Hemangiomas	U. V. Portmann, M.D.
12:10 p.m.	Surgical Management of Pruritus Ani et Vulvae	R. B. Turnbull, Jr., M.D.
12:30 p.m.	Luncheon—Courtesy of the Bunts Institute	
	Afternoon Session	
1:45 p.m.	Special Lecture—Subject to be announced	A. C. Curtis, M.D. (Guest)
2:30 p.m.	Common Superficial Fungus Infections	G. H. Curtis, M.D.
2:50 p.m.	Cutaneous Manifestations of Peripheral Vascular Disease	V. G. deWolfe, M.D.
3:10 p.m.	Moles, Keratoses, and Verrucae	J. R. Haserick, M.D.
3:30 p.m.	Urticaria	C. R. K. Johnston, M.D.
3:50 p.m.	Intermission	
4:00 p.m.	Stress Dermatoses	G. H. Curtis, M.D.
4:20 p.m.	Lupus Erythematosus	J. R. Haserick, M.D.
4:40-5:00 p.m.	Questions and Answers	

Thursday, October 30, 1952

Morning Session

9:00 a.m. . . . Papulosquamous Dermatoses: Psoriasis, Lichen Planus, Pityriasis Rosea . . . . . E. W. NETHERTON, M.D.

9:20 a.m. . . . Cutaneous Syphilis . . . . . G. H. CURTIS, M.D.

9:40 a.m. . . . Role of Plastic Surgery in Dermatologic Therapy . . . . . ROBIN ANDERSON, M.D.

10:10 a.m. . . . Surgical Lesions of Mouth and Pharynx . . . . . H. E. HARRIS, M.D.

10:30 a.m. . . . Intermission

10:45 a.m. . . . Cutaneous Manifestations of Common Virus Diseases . . . . . J. R. HASERICK, M.D.

11:00 a.m. . . . Acne Vulgaris and Rosacea . . . . . G. H. CURTIS, M.D.

11:20 a.m.-12:00 p.m. Noon Panel—Antibiotics . E. W. NETHERTON, M.D. (Moderator)
G. H. Curtis, M.D., J. R. Haserick, M.D.
C. R. K. Johnston, M.D., V. G. deWolfe, M.D.

Guest Speakers:

John E. Dunphy, M.D.—Associate Professor of Surgery, Harvard Medical School, Boston, Mass.

Donald M. Glover, M.D.—Director of Surgery, St. Luke's Hospital, and Associate Clinical Professor, Western Reserve University School of Medicine, Cleveland, Ohio.

Arthur C. Curtis, M.D.—Professor of Dermatology and Syphilology, University of Michigan Medical School, Ann Arbor, Mich.

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Please register me for the course on "Management of Common Dermatologic Problems" to be given October 29 and 30, 1952. (Registration Fee is $15.00, except for interns and residents, and members of the Armed Forces in uniform, who will be admitted free.)

I am enclosing check for $5.00 and the remainder will be paid on registration, October 29. Checks should be made payable to the Frank E. Bunts Institute.

Name .....

Address .....

Medical School and
Date of Graduation .....

This course is open only to graduates of approved medical schools.

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Please register me for the course on "Surgery of the Abdomen" to be given October 15 and 16, 1952. (Registration Fee is $15.00, except for interns and residents, and members of the Armed Forces in uniform, who will be admitted free.)

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Date of Graduation .....

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